Belgian
Red Cross
Flanders

Evidence summaries to support First Aid Guidelines

Edition 2016

Centre for Evidence-Based Practice
Belgian Red Cross-Flanders

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Introduction

The Red Cross/Red Crescent is thé **reference for first aid education** worldwide. First aid is a core activity of the 190 Red Cross and Red Crescent Societies and they are the major first aid educators and providers in the world. It is their mission to make people self-reliant in emergency situations or disasters and to strengthen community resilience. Millions of people are hurt or killed by injuries every year due to inadequate response or lack of timely assistance. Taking immediate action and applying the appropriate first aid techniques, can considerably reduce deaths and injuries, and the impact of disasters and everyday emergencies. The Red Cross therefore provides training courses in first aid, which are based on first aid guidelines.

Since 2005 Belgian Red Cross-Flanders (BRC-F) has played a **pioneering role in the development of first aid guidelines and manuals** using an **evidence-based approach** in accordance with international standards on Evidence-Based Medicine and evidence-based guideline development.
The overall aim is to introduce harmonized first aid education to the public, using effective guidelines and first aid techniques, supported by the latest medical and scientific evidence. As it targets lay people, the interventions must correspond to the target group's ability to learn and execute the proposed actions and have the objective of maintaining and improving the overall health outcome chances of the victim.

Evidence to support the guidelines is being identified by the BRC-F **Centre for Evidence-Based Practice (CEBaP)** (http://www.rodekruis.be/en/who-are-we/research/centre-for-evidence-based-practice/). The methodology used to develop these guidelines is based on the AGREE II approach (Brouwers et al., 2010) and is described in our methodological charter (De Buck et al., 2014). The methodology comprises the following steps:

(1) for each first aid/preventive intervention or risk factor, a PICO (Population, Intervention, Comparison and Outcome) question, or research question, is defined,
(2) for each PICO question a search strategy for different databases is composed,
(3) study selection is performed based on title and abstract in a first round, and full text screening (against predefined selection criteria) in a second round,
(4) data extraction of the included studies is performed and documented in an "evidence summary",
(5) the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology is used to assess limitations of study design for each individual study (Atkins et al., 2004), and to define a "level of evidence" for the body of evidence,
(6) draft first aid recommendations are formulated by the First Aid Service of BRC-F, based on the evidence provided in the evidence summaries, and taking into account the preferences of the target group and practice experience,
(7) final evidence-based first aid recommendations are formulated taking into account expert medical consensus from an expert panel including general practitioners and specialists, and the strength of the recommendations is determined,
(8) all guidelines are reviewed every five years so that the recommendations are up-to-date in line with the most recent scientific studies.

This approach resulted in the publication of the **European First Aid Manual** (EFAM) in 2006 (Van de Velde et al., 2007). In 2009 the project was extended to the Sub-Saharan African continent and in 2011 the **African First Aid Materials** (AFAM) became available to the public (Van de Velde et al., 2011). Also, evidence-based **Indian First Aid Guidelines** (IFAG) and materials for India were developed (De Buck et.

al, 2015). In addition, we reviewed our **first aid manual for Flanders**, Belgium '*Help! First aid for everyone*' in 2015-2016, as well as the manual for our emergency services, including advanced first aid interventions. For each of these guidelines, evidence was searched to specifically support local first aid interventions (e.g. honey for burn wounds in the African guidelines), in addition to "basic first aid interventions" which are included in each of the guidelines.

As an example, for the evidence-based guideline '*Help! First aid for everyone*' three databases (MEDLINE, using the PubMed Interface; Embase using the Embase.com interface and the Cochrane Library) were searched for the best available scientific evidence. In total **319 topic-specific evidence summaries** were developed, including 181 summaries about first aid interventions, 76 about preventive interventions, 6 on a combination of first aid and prevention, 46 about risk factors and 10 about diagnostics. A total of **11.8716 references** were screened. Title and abstract screening resulted in 2586 references of which the full texts were evaluated. 2009 studies were not eligible according to our in- and exclusion criteria. Finally, **533 studies** were included as a basis for the guidelines. Based on the evidence identified and taking into account practice considerations, the First Aid Service of BRC-F formulated draft recommendations. The evidence summaries and draft recommendations were presented at the Medical Committee of BRC-F which is composed of the provincial chief physicians of BRC-F, a physician of the Flemish Government and physicians of the department of Defense of the Belgian Government. They evaluated the recommendations and the evidence during six expert meetings. The experts decided whether or not to recommend certain interventions, taking into account the quality of the evidence, the feasibility, the benefits and harms of the intervention, and the costs. Then they formulated final recommendations, decided on the strength of the recommendation (weak or strong) and when appropriate, they also formulated 'Good Practice Points'.

In this book we provide all our **updated evidence summaries**, used as a basis for the first aid manual '*Help! First aid for everyone*', edition 2016, and our other first aid projects.

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Development of Evidence-Based First Aid Guidelines for Laypeople in Flanders, Belgium

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Abstract

Introduction: First aid training of laypeople is important to make people self-reliant in emergency situations or disasters and to strengthen community resilience.

Aim: The aim of this project was to develop a First Aid manual '*Help! First aid for everyone*' according to the Evidence-Based Practice methodology, including several first aid and preventive topics as well as risk factors.

Methods: Evidence-based guidelines were developed according to our methodological charter and the AGREE II checklist for guideline development. Three databases (MEDLINE, using the PubMed Interface; Embase using the Embase.com interface and the Cochrane Library) were searched for the best available evidence. The quality of identified evidence was assessed using the GRADE methodology. Draft recommendations were formulated and presented to a panel of medical experts.

Results: 319 topic-specific searches were performed. A total of 118716 references were screened out of which finally 533 studies were included as a basis for the guidelines. Two examples of effective interventions, keeping burn blisters intact and the use of hand sanitizers, are provided in detail.

Conclusion: Evidence-Based first aid and prevention guidelines were developed for Flanders. This manual will be used as a basis for the first aid courses provided by the Belgian Red Cross-Flanders.

Keywords: First aid; Prevention; Evidence-Based Practice; Laypeople

Introduction

The Red Cross/Red Crescent is the reference for first aid education worldwide. First aid is a core activity of the 190 Red Cross and Red Crescent Societies and they are the major first aid educators and providers in the world. It is their mission to make people self-reliant in emergency situations or disasters and to strengthen community resilience. Millions of people are hurt or killed by injuries every year due to inadequate response or lack of timely assistance. Taking immediate action and applying the appropriate first aid techniques can considerably reduce deaths and injuries, and the impact of disasters and everyday emergencies. The Red Cross therefore provides training courses in first aid, which are based on first aid guidelines.

According to the International Federation of Red Cross and Red Crescent Societies (IFRC), first aid is defined as "Immediate help provided to a sick and injured person until professional help arrives. It is concerned not only with physical injury or illness but also with other initial care, including psychosocial support for people suffering emotional distress from experiencing or witnessing a traumatic event. First aid interventions seek to preserve life, alleviate suffering, prevent further illness or injury and promote recovery" [1].

Qualitative guidelines should be based on solid scientific evidence, or in the absence of evidence, on expert consensus [2-4]. This can be accomplished by working according to the triad of Evidence-Based Practice, in which scientific literature is combined with the preferences of the target population and expert opinion [4]. This approach contributes to the harmonization of first aid guidelines for the general public.

Providing evidence-based first aid is an important pillar of the strategy of Belgian Red Cross-Flanders (BRC-F). We already developed several evidence-based guidelines and materials for Europe, Sub-Sahara Africa and India [5-7]. For each of these guidelines, evidence was searched to specifically support local first aid interventions (e.g. honey for burn wounds in the African guidelines), in addition to "basic first aid interventions" which are included in each of the guidelines. Furthermore, an evidence-based educational pathway was developed to include first aid in the school curriculum [8], and together with the Flemish government, guidelines concerning first aid for sports injuries were developed.

Five years ago, a first step was taken to publish a first aid manual for Flanders based on scientific evidence. Since guidelines need to be updated every five years, the aim of this project was to develop a first aid manual '*Help! First aid for everyone*' according to the latest methodology and scientific literature [4]. Furthermore, additional topics were reviewed so that not only first aid topics, but also preventive interventions and risk factors are now included. This handbook will be used as a basis for the first aid training courses provided by the BRC-F.

Methods

The evidence-based guidelines were developed according to our methodological charter and the AGREE II checklist for guideline development [4,9].

Selection of topics

The selection of relevant topics was based on the topics included in the previous version of the handbook. New topics were added based on input of the First Aid services of the BRC-F following feedback of first aid teachers. Topics included bleeding, skin wounds, burn wounds, animal bites and stings, injuries of the head and neck, chest, limbs, poisoning, accidents in the water, electrical and lightning injuries, problems with heat and cold, travel illnesses, allergies, pregnancy and delivery and infections. Evidence from the recently published first aid and resuscitation guidelines of the European Resuscitation Council (ERC) were incorporated for topics concerning resuscitation and choking, and from the first aid guidelines of the International Liaison Committee on Resuscitation (ILCOR) [2,3,10]. Consistency of our guidelines with the IFRC guidelines, which we co-developed, was revised.

Search strategy

For each first aid/preventive intervention or risk factor, a PICO (Population, Intervention, Comparison, and Outcome) question was defined and a search strategy was composed. Three databases (MEDLINE, using the Pub Med Interface; Embase, using the Embase.com interface, and the Cochrane Library) were searched for the best available evidence between the dates of inception until the search date (2015). Study selection was performed by one reviewer (VB, HVR or EDB). A first selection of studies was made by screening title and abstract. Full texts were retrieved for relevant studies and checked if they met the in- or exclusion criteria. The reference lists of included articles were scanned for other potentially relevant studies, as well as the first 20 related citations in Pub Med. For each PICO question an "evidence summary" was developed, in which the search strategies were documented.

Selection criteria

The following in- and exclusion criteria were applicable for all first aid or preventive interventions or risk factors:

Population: Sick or injured people or healthy volunteers of all ages.

Intervention/Risk factor: Inclusion of interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional, the study is included in case no other evidence with laypeople is available (but considered as indirect evidence). Interventions that require special equipment or competences were excluded, as well as interventions that do not take place during the acute phase which can be considered as aftercare. For risk factors, we included modifiable, proximal risk factors with a potential immediate implication for practice that results in primary prevention at the household or community level and risk factors related to healthy persons. Risk factors that lead to interventions with already proven effectiveness were excluded. Furthermore, risk factors that do not precede the outcome and risk factors that are common sense were excluded.

Outcome: Studies describing health-related outcome measures including survival, functional recovery, pain, complications, and time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or adverse effects were included. Studies measuring performance by basic first responders or lay caregivers and/or community health workers were excluded.

Study design: Systematic reviews: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. Experimental studies: inclusion in case of one of the following study types: (quasi or non-) randomized controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. Observational studies: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Following study types were excluded: case series, cross-sectional studies, animal studies, *ex vivo* or *in vitro* studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no standard deviations, effect sizes or p-values.

Language: Only articles in English were included.

Publication year: We searched the databases from time of inception until the search date in 2015.

In addition to these general selection criteria, specific in- and exclusion criteria were formulated for each PICO question.

No PICO question was formulated if the intervention concerned (1) a 'Good Practice Point' ("Good Practice Points are intended to assist guideline users by providing short pieces of advice which may not have an evidence base, but which are seen as essential to good clinical practice", according to the definition of the Scottish Intercollegiate Guidelines Network [11]) or common sense, (2) the responsibility of professionals (such as a medical doctor or pharmacist), (3) interventions with only a long-term effect (e.g. lifestyle interventions such as healthy diet, smoking cessation), (4) the practical organization of activities, (5) medico-legal aspects (e.g. use of EpiPen) or (6) anatomy or physiology. For risk factors, no PICO question was formulated if the risk factor did not precede the outcome, was common sense, a fixed marker (e.g. race, gender), a distal risk factor (e.g. smoking as a risk factor for lung cancer) or not valid for healthy people.

Data extraction

Data concerning study design, population, outcome measures, effect sizes and quality of the study were collected. Review Manager 5 [12] was used to calculate effect sizes (risk ratios (with 95% confidence intervals) for dichotomous variables and mean differences (with 95% confidence intervals) for continuous outcomes) if these were not reported in the study and raw data were available. A p-value <0.05 was considered as statistically significant.

Quality assessment

The GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach was used to assess limitations of study design for each individual study, followed by a quality rating for the body of evidence, which depends on study limitations, imprecision, inconsistency, indirectness and publication bias and ranges from high to very low. The initial level for experimental studies is 'high-quality' whereas observational studies start from a 'low-quality' level. A high level of the body of evidence means that "further research is very unlikely to change our confidence in the estimate of effect" whereas a low level of evidence indicates that "further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate" [12].

Formulation of evidence-based recommendations

Based on the evidence identified and taking into account practice considerations, the First Aid Service of BRC-F formulated draft recommendations. The evidence summaries and draft recommendations were presented at the Medical Committee of BRC-F which is composed

of all provincial chief physicians of BRC-F, a physician of the Flemish Government and physicians of the department of Defense of the Belgian Government. They evaluated the recommendations and the evidence during six expert meetings. The experts decided whether or not to recommend certain interventions, taking into account the quality of the evidence, the feasibility, the benefits and harms of the intervention, and the costs. Then they formulated final recommendations, decided on the strength of the recommendation (weak or strong) and when appropriate, they also formulated 'Good Practice Points'.

The draft recommendations were also reviewed by a reading group consisting of staff members of the First Aid Services, the Relief Services and the Centre for Evidence-Based Practice of BRC-F as well as first aid teachers and laypeople.

Results

Characteristics of studies

We performed 319 topic specific searches. For each topic, a PICO (Population, Intervention, Comparison, and Outcome) question was defined (see below for 2 examples). 181 PICOs concerned first aid, 76 were about prevention, 6 PICOs defined a combination of first aid and prevention, 46 were about risk factors and 10 diagnostic PICOs were formulated. The searches resulted in a total of 118716 references. Title and abstract screening resulted in 2586 references of which the full texts were evaluated. 2009 studies were not eligible according to our in- and exclusion criteria. Finally, 533 studies or systematic reviews were included for data extraction. The flowchart in figure 1 shows an overview of the study selection for all PICO questions together. For 128 PICO questions (100 first aid interventions, 14 on prevention, 11 on risk factors and 3 diagnostic PICOs) no evidence was found. When searching for evidence we always first searched for existing systematic reviews. Of the 191 PICOs for which evidence was found, the evidence for 72 PICOs was based on systematic reviews, of which 41 included Cochrane reviews. 24 evidence summaries were based on Cochrane reviews as a whole, whilst for 4 PICOs a Cochrane review was used but an update was also performed because the review was out-of-date (more than 5 years old). For 13 PICOs, Cochrane reviews were used as a source of individual studies. If no existing systematic reviews were available, a search for individual studies was performed.

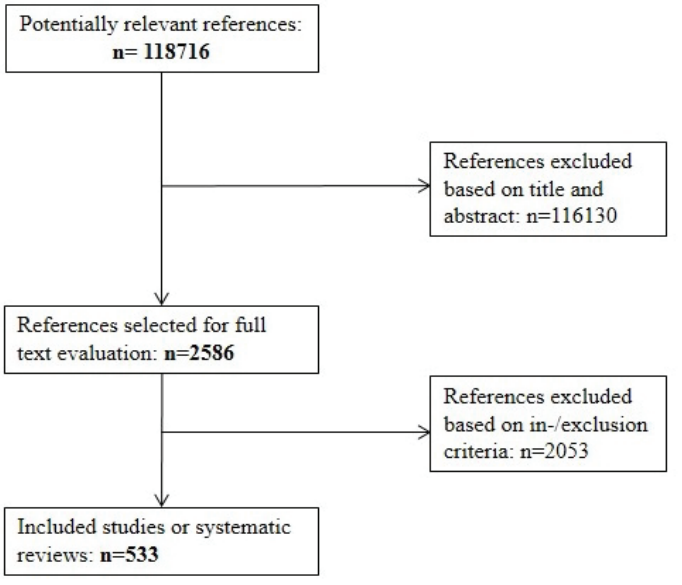

Figure 1: Overview of study selection for all 319 PICO questions together.

From evidence to recommendations: two detailed examples

An example of an effective first aid intervention is keeping burn blisters intact. An example of an effective preventive intervention is the use of hand alcohol as prevention of diarrhea. These two examples are described in detail below.

Example 1: Deroofing or aspiration of burn blisters: The following PICO question was formulated: In humans with burns (P), is deroofing or aspiration of blisters (I) compared to leaving the blisters intact (C) effective to change tissue healing, functional recovery, pain, complications, time to resumption of usual activities, restoration to the pre-exposure condition, time to resolution of symptoms (O)?

A total of 910 studies were identified with the search strategy which can be found in supplemental file 1. Finally, only one study was included [13]. This study includes 202 patients with 316 minor burns. Only thermal burns of the arms and legs that could be treated with paraffin gauze dressings were included. Burn blisters were aspirated after one day, deroofed after one day or kept intact for 10 days (table 1).

It was shown that keeping the blister intact resulted in a statistically significant lower number of blisters colonized with any bacterium or with *Staphylococcus aureus* specifically compared to aspirating or deroofing the blister (table 2) [13]. The level of evidence is low due to limitations in study design (no information on randomization or blinding) and imprecision due to limited sample size (n<400). This means that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate [14].

Finally, based on the identified evidence, draft recommendations were formulated and discussed/reviewed by the expert panel. The final recommendation was formulated as follows: "Do not puncture burn blisters. This will increase the risk of infection. Because of the burn, the protective effect of the skin is compromised, which allows micro-organisms to penetrate the body. This could slow down the recovery."

Example 2: Hand sanitizers as preventive measure for diarrhea: In our first aid manual, it is recommended to wash hands with water and soap before and after providing first aid. However, what if no water is available? Is the use of hand alcohol a good alternative? To answer this question, the following PICO question was formulated: In humans (P), is the use of hand sanitizers (I) compared to no intervention (C) effective to prevent diarrhea (O)?

A total of 390 studies were identified with the search strategy which can be found in supplemental file 2. After title and abstract screening, 18 studies were assessed based on the full text. Finally, 2 randomized controlled trials were included [15,16] One study was performed among 134 administrative officers in Germany who did not already apply hand hygiene at work. They were randomized into an intervention or a control group. The second study was performed among 1364 students in six schools in Nairobi, Kenya. The schools were randomly assigned to receive one of the interventions (hand washing with soap or hand sanitizer) or the control (no intervention) (table 3).

Author	Study Design	Population	Comparison
Swain et al. [13]	Experimental: Non-randomized controlled trial	202 patients with 316 minor burns. Only thermal burns of the arms and legs that could be treated with paraffin gauze dressings were included.	Intervention 1: Aspiration after 1 day Intervention 2: Deroofing after 1 day Control: keeping blister intact for 10 days

Table 1: Characteristics of included studies for evidence review concerning deroofing or aspiration of burn blisters.

It was shown that the use of alcohol-based hand sanitizers resulted in a statistically significant decrease of absenteeism due to diarrhea, compared to the usual unchanged hand hygiene practices [15]. Furthermore, it was shown that alcohol-based hand sanitizers resulted in a statistically significant decrease of the number of watery stools in 24 hours compared to hand washing with soap [16]. However, a statistically significant decrease of diarrhea, using alcohol-based hand rubs compared to unchanged hand hygiene, no intervention or hand washing with soap, could not be demonstrated [15,16]. Furthermore, a statistically significant decrease of any loose/watery stools in 24 hours, using alcohol-based hand sanitizer compared to no intervention, could not be demonstrated (table 4) [16].

Evidence is of low quality due to imprecision (limited sample size and large variability of results) and possible publication bias, since in one study one author is employed by the manufacturer of the hand gels and 2 authors received financial support for research from the manufacturer.

Outcome	Comparison	Effect Size	#Studies, # Participants	Reference
Number of blisters colonized with bacteria	Deroofing *vs* Keeping blister intact	Statistically significant: 78/102 *vs* 15/110 § RR: 5.61, 95%CI [3.46; 9.08] (p<0.00001)* *In favor of keeping blister intact*	1, 102 *vs* 110 blisters	Swain et al. [13]
Number of blisters colonized with *Staphylococcus aureus*		Statistically significant: 45/102 *vs* 2/110 § RR: 24.26, 95%CI [6.04; 97.47] (p<0.00001)* *In favor of keeping blister intact*		
Number of blisters colonized with bacteria	Aspiration *vs* keeping blister intact	Statistically significant: 73/104 vs 15/110 § RR: 5.15, 95%CI [3.16; 8.37] (p<0.00001)* *In favor of keeping blister intact*	1, 104 *vs* 110 blisters	
Number of blisters colonized with *Staphylococcus aureus*		Statistically significant: 19/104 *vs* 2/110 § RR: 10.05, 95%CI [2.40; 42.08] (p=0.004)* *In favor of keeping blister intact*		

Table 2: Synthesis of findings for evidence review concerning deroofing or aspiration of burn blisters.
*Calculations done by the reviewer (s) using Review Manager software, § Imprecision (low number of events)

Author	Study Design	Population	Comparison
Hübner et al. [15]	Experimental: Randomized controlled trial	134 administrative officers who do not already apply hand disinfection at work were randomized in control (n=67, mean age 45.6 years) and intervention (n=67, mean age 43.6 years) group.	Intervention: Alcohol-based hand rubs. Participants were advised to use it at least five times daily, especially after toilet use, blowing nose, before eating and after contact with ill colleagues, customers and archive material. Control: Unchanged daily hand hygiene.
Pickering et al. [16]	Experimental: Randomized controlled trial	1364 students (ages 5-13) in 6 schools in Nairobi, Kenya. Schools were randomly assigned to receive a hand washing with soap intervention (n=460), an alcohol-based hand sanitizer intervention (n=435) or no intervention (n=469)	Interventions: (1) Hand washing with soap or (2) Alcohol-based hand sanitizer: an initial teacher training session followed by the installation of soap or sanitizer wall dispensers. Control: no intervention

Table 3: Characteristics of findings for evidence review concerning the use of hand sanitizers as a preventive measure for diarrhea.

Outcome	Comparison	Effect Size	#Studies, #Participants	Reference
Absenteeism due to diarrhea	Alcohol based hand rubs *vs* unchanged hand hygiene	Statistically significant: 1/64 *vs* 8/65 § OR: 0.11, 95%CI [0.01;0.93] (p<0.05) *In favor of alcohol-based hand rubs*	1, 64 *vs* 65	Hubner et al. [15]
Diarrhea		Not statistically significant: 8/64 *vs* 15/65 § OR: 0.48, 95%CI [0.19;1.22] (p ≥ 0.05)		
	Alcohol-based hand sanitizer *vs* no intervention	Not statistically significant: RR: 0.75, 95%CI [0.52; 1.10] (p=0.14) ¥	1, 460 *vs* 435 *vs* 469	Pickering et al. [16]
	Alcohol-based hand sanitizer *vs* hand washing with soap	Not statistically significant: RR: 0.89, 95%CI [0.61; 1.30] (p=0.56) ¥		
Any loose/watery stool in 24 hours	Alcohol-based hand sanitizer *vs* no intervention	Not statistically significant: RR: 0.87, 95%CI [0.72; 1.04] (p=0.12) ¥		
	Alcohol-based hand sanitizer *vs* hand washing with soap	Statistically significant: RR: 0.80, 95%CI [0.67; 0.95] (p=0.01) *In favor of alcohol-based hand sanitizer*		

Table 4: Synthesis of findings for evidence review concerning the use of hand alcohol as a preventive measure for diarrhea
*Calculations done by the reviewer (s) using Review Manager software, § Imprecision (low number of events); ¥ Imprecision (large variability of results)

In the first aid manual, it is recommended to wash the hands with water and soap before and after providing first aid and if the hands are visibly dirty. However, if no water is available, hand sanitizers can be recommended based on the evidence described above. The recommendation was formulated as follows: "If no water is available, or your hands are not visibly dirty, decontaminate your hands with a hand sanitizer before and after taking care of a casualty."

Discussion

An evidence-based first aid handbook was developed for the Belgian context. For this project, a total of 118716 references were screened and 533 studies were finally included. Based on the evidence, draft recommendations were formulated which were presented to an expert panel.

The strengths of this project are that no search limits such as geographical filters or time constraints were used. The evidence was searched according to a strict methodology and the AGREE II checklist for guideline development was followed [4,9]. For 23% of the topics, a systematic review was identified and included, either as a whole or as a source of individual studies, of which 13% were Cochrane reviews. Furthermore, evidence from recently published international first aid and resuscitation guidelines of ILCOR and the ERC were also incorporated in the manual [2,3,10,17,18]. In addition, for some topics our evidence summaries were incorporated in the IFRC first aid guidelines which will be published soon. All steps of the methodology of Evidence-Based Practice were followed. The best available scientific evidence was combined with the preferences of the target population and the expert opinion of the Medical Committee of BRC-F.

However, this project also has some limitations. For this version of the manual, the focus was on first aid and prevention interventions and possible risk factors. Only 10 diagnostic PICOs were formulated. However, in the manual each topic starts with a section explaining the signs and symptoms of the injury or illness. During the next update of the manual in 5 years, it is planned to include these diagnostic topics to fully support the signs and symptoms sections with scientific evidence. Another limitation is the lack of evidence for 40% of the topics. Recommendations for these topics were therefore based on 'Good Practice Points' and expert opinion. This big lack of evidence indicates that more primary research is definitely needed in first aid settings and pre-hospital care.

In conclusion, an evidence-based manual for first aid was developed. This manual will be used as guidance for the first aid courses provided by the Belgian Red Cross-Flanders. The 762 volunteer first aid teachers will be retrained so they can teach first aid to more than 20000 people each year according to the latest scientific evidence. Furthermore, the handbook will also be broadly available for anyone with an interest in first aid. In addition, all evidence summaries will be made available upon request. In this way we try to promote first aid knowledge and skills and helping behavior among the general population as much as possible.

Authors Contribution

All authors contributed significantly to this work. PV proposed the guideline project. AV coordinated the project. VB wrote the manuscript. VB, HVR and EDB performed the evidence reviews. All authors have critically reviewed the manuscript.

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Matthieu Clarysse, of the First Aid Department, drafted the recommendations and processed the feedback of the expert panel and the reading group. The medical committee of BRC-F consisted of: Prof. Dr. P. Broos (Prof. Em. KU Leuven, Chairman of the panel), Dr. Pascal Vranckx (Medical director Cardiac ITU, Jessa Hospital Hasselt, Belgium), Dr. Karel Vandevelde (AZ St Jan Brugge, Belgium), Dr. Evi Steen (anaesthetist-uregentist, UZ Gent, Belgium), Dr. Marc Vanpoecke (General Practitioner), Dr. Pieter Mertens (anaesthesiologist at University Hospital Antwerp, Belgium), Dr. Jan Van Heuverswyn (Chief Advisor at Flemish Government, Department of Economy, Science and Innovation), Dr. Ive Van Cauwenbergh (Medical Doctor at Belgian Defence) and Dr. Erwin Dhondt (Medical Doctor at Belgian Defence).

Finally, we would like to thank all members of the reading group for their feedback on the draft guidelines.

Competing Interest

All authors are employees at Belgian Red Cross-Flanders and receive no other funding. One of the activities of Belgian Red Cross-Flanders is providing first aid training to laypeople.

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BASIC PRINCIPLES

Hygienic measures – Respiratory Illness (Prevention)

Question (PICO)	In humans (P), which hygienic measures (I) compared to other hygienic measures (C) are effective to prevent respiratory illness (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "hand disinfection"] OR handwash*:ti,ab,kw OR "hand wash*":ti,ab,kw OR "hand hygiene":ti,ab,kw or "hand sterility":ti,ab,kw OR [mh "hand sanitizers"] OR "hand cleans*":ti,ab,kw OR "hand gel*":ti,ab,kw OR "hand sanitiz*":ti,ab,kw 2. [mh "respiratory tract diseases"] OR [mh influenza] OR respiratory:ti,ab,kw OR influenza:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "hand disinfection"[Mesh] OR Hand wash*[TIAB] OR hand disinfect*[TIAB] OR hand clean*[TIAB] OR hand hygiene[TIAB] OR "Hand Sanitizers"[Mesh] OR hand gel*[TIAB] OR hand sanit*[TIAB] 2. "Respiratory Tract Infections"[Mesh] OR respiratory[TIAB] OR "Influenza, Human"[Mesh] OR influenza[TIAB] 3. ((((((((((Meta-Analysis as Topic[Mesh])) OR ((meta analy*[TIAB]))) OR ((metaanaly*[TIAB]))) OR ((Meta-Analysis[Publication Type]))) OR ((systematic review*[TIAB] OR systematic overview*[TIAB]))) OR ((Review Literature as Topic[Mesh])))) OR ((cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB]))) OR ((reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB]))) OR ((((selection criteria[TIAB] OR data extraction[TIAB])) AND ((Review[PT]))))) NOT ((Comment[PT] OR Letter[PT] OR Editorial[PT] OR animal[Mesh] NOT (animal[Mesh] AND human[Mesh]))) 4. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'hand washing'/exp OR 'hand washing':ab,ti OR 'hand disinfection':ab,ti OR 'hand cleansing':ab,ti OR 'hand hygiene':ab,ti OR 'hand sterility':ab,ti OR 'hand sanitization':ab,ti OR 'hand sanitizer'/exp OR 'hand sanitizer':ab,ti OR 'hand gel':ab,ti 2. 'respiratory tract infection'/exp OR 'influenza'/exp OR respiratory:ab,ti OR influenza:ab,ti 3. 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti 4. 1-2 AND Guidelines, systematic reviews, retrieved with the above searches, and used as source for individual studies: Jefferson, 2011 Warren-Gash, 2012

	Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	22 April 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. Nose wash and disinfection of living quarters are excluded since these are not measures we deem valuable for lay first aiders. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. If a certain intervention is covered by RCTs or pooled observational studies, no extra individual observational studies will be searched. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison/Risk factor	Remarks
Carabin, 1999, Canada	Experimental: randomized controlled trial	1729 children aged 18 to 36 months in 47 day care centres.	Intervention: training session (1 day) with washing of hands, toy cleaning, window opening, sand pit cleaning and repeated exhortations to hand wash Control: no training	cited in SR Jefferson 2011
Jefferson, 2011, Italy	Systematic Review	66 papers of 67 studies	different hygienic measures vs other hygienic measures or no intervention	
Kotch, 1994, USA	Experimental: randomized controlled trial	389 children aged <3 years in daycare for at least 20 hours per week	Intervention: Structured hand washing and environment disinfecting program with waterless disinfectant scrub Control: no intervention	cited in SR Jefferson 2011

Ladegaard, 1999, Denmark	Experimental: randomized controlled trial	475 children between 0 and 6 years old in child care centres	Intervention: multifaceted: training and information on hand washing	cited in SR Jefferson 2011 and Warren-Gash 2012
Luby, 2005, USA	Experimental: randomized controlled trial	3168 children younger than 15 years in squatter settlements in Pakistan. 1523 children were assigned to use antiseptic soap, 1640 children were assigned to use plain soap and 1528 children continued their usual behaviour	Intervention 1: hand washing with antiseptic soap Intervention 2: hand washing with plain soap Control: usual behaviour	cited in SR Jefferson 2011 and Warren-Gash 2012
Morton, 2004, USA	Experimental: Randomized controlled trial (within subjects)	253 children (120 girls, 133 boys) from kindergarten to 3rd grade.	Intervention: use of an alcohol gel as an adjunct to regular hand washing and educational program Control: regular hand washing and educational program	cited in SR Jefferson 2011
Roberts, 2000, Australia	Experimental: randomized controlled trial	558 children (aged <3 years) attending child care centres at least 3 days a week. 299 children in the intervention arm vs 259 children in the control arm	Hand washing program with training for staff and children vs no hand washing program	cited in SR Jefferson 2011 and Warren-Gash 2012
Sandora, 2005, USA	Experimental: randomized controlled trial	292 families with 1 or more children (aged 6 months to 5 years) who were in child care for 10 or more hours a week. 155 children were allocated to the intervention arm, 137 children were allocated to control arm	Intervention: Alcohol-based hand sanitiser with bi-weekly hand hygiene educational materials over 5 months Control: bi-weekly educational material on healthy diet	cited in Jefferson 2011 and Warren-Gash 2012
White, 2001, USA	Experimental: randomized controlled trial	769 children, aged 5 to 12 of 32 classes (16 classes in each arm). 388 used pump-activated antiseptic hand rub and 381 used placebo	Intervention: Pump-activated antiseptic hand rub Control: inert placebo	cited in Jefferson 2011 and Warren-Gash 2012
Wong, 2013, China	Systematic Review	10 studies, 8 in developed and 2 in developing countries	Hand washing or Hand washing and facemask vs no intervention	

Synthesis of findings

Outcome	Comparison/Risk factor	Effect Size	#studies, # participants	Reference
Hand hygiene				
SARS	Frequent hand washing (minimum 11 times daily) vs no	Statistically significant: 259/666 vs 1224/2159	7, 666 vs 2159	Jefferson, 2011

	frequent hand washing (less than 11 times daily)	OR: 0.54, 95%CI [0.44; 0.67], p<0.00001 *In favour of frequent hand washing*		
Incidence of colds (incidence rate ratio)	training on hand washing and other hygienic measures vs usual behaviour	Statistically siginificant: RR: 0.80, 95%CI [0.68; 0.93] p=0.0071 *In favour of hand washing*	1, 843 vs 750	Carabin, 1999
acute respiratory illness	hand washing and environment disinfection program vs no intervention	Not statistically significant: RR: 0.94, 95%CI [-2.43; 0.66] ¥	1, 371 (not stated how many in each group)	Kotch, 1994
Sore throat or cold	information and training on hand washing vs no intervention	Not statistically significant: 29/212 vs 45/263 RR: 0.80, 95%CI [0.52; 1.23], p=0.31¥	1, 212 vs 263 §	Ladegaard, 1999
Rates of cough or difficulty breathing	plain soap vs usual behaviour	Statistically significant: RR: 0.49, 95%CI [0.35; 0.63], p<0.00001 *In favour of plain soap*	1, 1640 vs 1528	Luby, 2005
School absenteeism	Hand sanitizer + hand washing vs hand washing alone	Statistically significant: odds of absenteeism due to infectious illness reduced by 43% p=0.0053 £ *In favour of hand sanitizer*	1, 253 § (within subjects)	Morton, 2004
	Antiseptic hand rub vs placebo	Statistically significant: RR: 0.67, 95%CI [0.49; 0.91], p=0.0121 *In favour of antiseptic hand rub*	1, 388 vs 381	White, 2001
Upper respiratory tract secondary transmission rate	Alcohol-based hand sanitizer vs no hand sanitizer	Not statistically significant: RR: 0.97, 95%CI [0.72; 1.30], p=0.841¥	1, 155 vs 137 §	Sandora, 2005
Upper respiratory tract infection rate	Hand washing program vs no hand washing program	Not statistically significant: RR: 0.95, 95%CI [0.89; 1.01], p=0.1233	1, 299 vs 259	Roberts, 2000
Laboratory-confirmed influenza	Hand washing vs no hand washing	Not statistically significant: 101/2982 vs 119/3053 RR: 0.90, 95%CI [0.67; 1.20], p=0.47¥	4, 2982 vs 3053	Wong, 2013
Influenza-like illness		Not statistically significant: 188/3046 vs 218/3118 RR: 0.86, 95%CI [0.71; 1.04], p=0.11¥	4, 3046 vs 3118	
Gloves				
SARS	Wearing gloves vs not wearing gloves	Statistically significant: 96/272 vs 899/1564 OR: 0.32, 95%CI [0.23; 0.45], p<0.00001 *In favour of wearing gloves*	6, 272 vs 1564	Jefferson, 2011
Wearing masks				
SARS	wearing mask vs not wearing mask	Statistically significant: 268/681 vs 1573/2535 OR: 0.32, 95%CI [0.26; 0.39], p<0.00001 *In favour of wearing mask*	7, 681 vs 2535	Jefferson, 2011
	Wearing N95 respirator vs not wearing N95 respirator	Statistically significant: 5/100 vs 146/717	3, 100 vs 717 §	

		OR: 0.17, 95%CI [0.07; 0.43], p=0.00020 *In favour of wearing N95 respirator*		
Wearing goggles				
SARS	goggles or mask with goggles vs no intervention	Statistically significant: 15/219 vs 370/1263 OR: 0.10, 95%CI [0.05; 0.17], p<0.00001 *In favour of goggles*	3, 219 vs 1263	Jefferson, 2011
Wearing gown				
SARS	wearing gown vs not wearing gown	Statistically significant: 83/242 vs 717/1218 OR: 0.33, 95%CI [0.24; 0.45], p<0.00001 *In favour of wearing gown*	5, 242 vs 1215	Jefferson, 2011
Combined interventions				
SARS	hand washing, masks, gloves and gowns vs no intervention	Statistically significant: 2/38 vs 113/331 OR: 0.09, 95%CI [0.02; 0.35], p=0.00051 *In favour of combined interventions*	2, 38 vs 331 §	Jefferson, 2011
Laboratory-confirmed influenza	Hand washing and facemask vs no intervention	Statistically significant: 62/1928 vs 92/2122 RR: 0.73, 95%CI [0.53; 0.99], p=0.04 *In favour of hand washing and facemask*	5, 1928 vs 2122	Wong, 2013
Influenza-like illness	Hand washing and facemask vs no intervention	Statistically significant: 176/1979 vs 272/2187 RR: 0.73, 95%CI [0.60; 0.89], p=0.002 *In favour of hand washing and facemask*	5, 1979 vs 2187	Wong, 2013

Mean ± SD (unless otherwise indicated)

* Calculations done by the reviewer(s) using Review Manager software

£ No raw data/SD's available, effect size and CI cannot be calculated [only if applicable for more than one cell]

¥ Imprecision (large variability of results), § Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Carabin, 1999	unclear, not described	yes, but not possible	yes (see Jefferson 2011)	yes, denominators unclear and not explained	
Kotch, 1994	unclear, not reported	yes, but not possible	yes, 18 families were dropped, denominator not clear	yes, denominators not clearly reported	
Ladegaard, 1999	unclear, not reported	yes, but not possible	yes, no total numbers of children included in each arm reported	yes, Limited data reported, especially denominators missing	

Luby, 2005	No (see Jefferson 2011)	yes, not blinded	unclear, 89% of the study population followed up, but no data on the clusters	No, "At baseline, households in the three intervention groups were similar."	
Morton, 2004	unclear	unclear	unclear	unclear	
Roberts, 2000	unclear, not reported	yes, but not possible	unclear, recruitment rate 88% (23 of 26 CCCs); loss to follow up not clear as no denominator given	No, centres comparable at baseline	
Sandora, 2005	No, opaque envelopes	Yes, but not possible	No, attrition was 15 in intervention arm and 19 in the control arm. ITT analysis was carried out	Unclear, well reported	
White, 2001	Unclear, not described	No, randomised by classroom and placebo hand rub was identical to active ingredient	Yes, partial reporting of outcomes, numerators and denominators	Yes, poor reporting	

Hand hygiene	**Initial grading High [A]**	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	[Limited sample sizes/large variability of the results]
Inconsistency	0	
Indirectness	0	
Publication bias	0	[Conflict of interest]
QUALITY (GRADE)	**Final grading Low [C]**	

Gloves	**Initial grading High [A]**	Downgrading due to
Limitations of study design	-1	See systematic review of Jefferson 2011
Imprecision	0	
Inconsistency	0	
Indirectness	0	
Publication bias	0	[Conflict of interest]
QUALITY (GRADE)	**Final grading Moderate [B]**	

Masks	**Initial grading High [A]**	Downgrading due to
Limitations of study design	-1	See systematic review of Jefferson 2011
Imprecision	-1	
Inconsistency	0	
Indirectness	0	
Publication bias	0	[Conflict of interest]
QUALITY (GRADE)	**Final grading Low [B]**	

Wearing goggles	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See systematic review of Jefferson 2011
Imprecision	0	
Inconsistency	0	
Indirectness	0	
Publication bias	0	[Conflict of interest]
QUALITY (GRADE)	**Final grading Moderate [B]**	

Wearing gown	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See systematic review of Jefferson 2011
Imprecision	0	
Inconsistency	0	
Indirectness	0	
Publication bias	0	[Conflict of interest]
QUALITY (GRADE)	**Final grading Moderate [B]**	

Combined interventions	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See systematic reviews of Jefferson 2011 and Wong 2013
Imprecision	0	
Inconsistency	0	
Indirectness	0	
Publication bias	0	[Conflict of interest]
QUALITY (GRADE)	**Final grading Moderate [B]**	

Conclusion	**Hand washing**: There is limited evidence from 8 experimental studies and 2 systematic reviews in favour of hand washing. (Although hand washing does not show significant changes in all outcomes, we place higher value in the fact that hand hygiene measures do show a significant reduction of most outcomes) It was shown that frequent hand washing resulted in a statistically significant decrease of SARS, compared to no frequent hand washing (Jefferson 2011). It was shown that training on hand washing resulted in a statistically significant decrease of incidence of cold, compared to no training on hand washing (Carabin 1999). It was shown that the use of plain soap resulted in a statistically significant decrease of the rate of cough or difficulty breathing, compared to usual behaviour (Luby 2005). It was shown that the use of hand sanitizer or antiseptic hand rub resulted in a statistically significant decrease of school absenteeism, compared to no hand sanitizer or placebo (Morton 2004, White 2001). A statistically significant change of sore throat or cold, acute respiratory illness, upper respiratory tract infection rate, laboratory confirmed influenza of influenza-like illness, using hand hygiene measures compared to no hand hygiene measures, could not be demonstrated (Kotch 1994, Ladegaard 1999, Sandora 2005, Roberts 2000, Wong 2013). Evidence is of low quality and results cannot be considered precise due to limited sample size, lack of data and/or large variability of results. **Gloves**: There is evidence from 1 systematic review in favour of using gloves. It was shown that wearing gloves resulted in a statistically significant decrease of SARS, compared to not wearing gloves (Jefferson 2011). Evidence is of moderate quality. **Masks**: There is limited evidence from 1 systematic review in favour of using masks. It was shown that wearing masks or N95 respirators resulted in a statistically significant decrease of SARS, compared to no masks or N95 respirators (Jefferson 2011).

	Evidence is of low quality and results cannot be considered precise due to low number of events. **Goggles**: There is evidence from 1 systematic review in favour of using goggles. It was shown that wearing goggles resulted in a statistically significant decrease of SARS, compared to not wearing goggles (Jefferson 2011). Evidence is of moderate quality. **Gown**: There is evidence from 1 systematic review in favour of wearing a gown. It was shown that wearing a gown resulted in a statistically significant decrease of SARS, compared to not wearing a gown (Jefferson 2011). Evidence is of moderate quality. **Combined interventions**: There is evidence from 2 systematic reviews in favour of combined hygienic measures. It was shown that a combination of hand washing, masks, gloves and gowns resulted in a statistically significant decrease of SARS, compared to no intervention (Jefferson 2011). It was shown that a combination of hand washing and facemasks resulted in a statistically significant decrease of laboratory-confirmed influenza and influenza-like illness, compared to no intervention (Wong 2013). Evidence is of moderate quality.
Reference(s)	**Articles** Carabin H, Gyorkos TW, Soto JC, Joseph L, Payment P, Collet JP. *Effectiveness of a training program in reducing infections in toddlers attending day care centers*. Epidemiology 1999, 10(3):219-27 Kotch JB, Weigle KA, Weber DJ, Clifford RM, Harms TO, Loda FA, Gallagher PN Jr, Edwards RW, LaBorde D, McMurray MP, et al. *Evaluation of an hygienic intervention in child day-care centers.* Pediatrics 1994;94(6 Pt 2):991–4. Ladegaard MB, Stage V. *Hand hygiene and sickness among small children attending day care centres. An interventional study*. Ukesgrift von Laeger 1999, 161:4396–400. Luby SP, Agboatwalla M, Feikin DR, Painter J, Billhimer W, Altaf A, Hoekstra RM. *Effect of handwashing on child health: a randomised controlled trial*. Lancet 2005, 366(9481): 225–33. Morton JL, Schultz AA. *Healthy hands: use of alcohol gel as an adjunct to handwashing in elementary school children*. Journal of School Nursing 2004, 20(3):161–7. Roberts L, Smith W, Jorm L, Patel M, Douglas RM, McGilchrist C. *Effect of infection control measures on the frequency of upper respiratory infection in child care: a randomised controlled study*. Pediatrics 2000, 105:738–42. Sandora TJ, Taveras EM, Shih MC, Resnick EA, Lee GM, Ross-Degnan D, Goldmann DA. *A randomized, controlled trial of a multifaceted intervention including alcohol-based hand sanitizer and hand-hygiene education to reduce illness transmission in the home*. Pediatrics 2005, 116(3):587–94. White CG, Shinder FS, Shinder AL, Dyer DL. *Reduction of illness absenteeism in elementary schools using and alcohol-free instant hand sanitizer*. Journal of School Nursing 2001, 17(5):258–65. **Systematic reviews** Jefferson T, Del Mar CB, Ferroni E, Al-Ansary LA, Bawazeer GA, van Driel ML, Nair S, Jones MA, Thorning S, Conly JM. *Physical interventions to interrupt or reduce the spread of respiratory viruses*. Cochrane Database of Systematic Reviews 2011, Issue 7, Art. No. CD006207 Warren-Gash C, Fragaszy E, Hayward AC. *Hand hygiene to reduce community transmission of influenza and acute respiratory tract infection: a systematic review*. Influenza and Other Respiratory Viruses 2012, 7(5):738-749 Wong VWY, Cowling BJ, Aiello AE. *Hand hygiene and risk of influenza virus infection in the community: a systematic review and meta-analysis*. Epidemiol Infect 2014, 142:922-932

Wound management - Wearing gloves for bleeding effects for care givers (First Aid)

Question (PICO)	In people treating people with penetrating injuries (P), does wearing gloves during treatment (I), compared to not wearing gloves (C), influence the rate of infection (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "lacerations"] OR [mh "hemorrhage"] OR laceration*:ti,ab,kw OR hemorrhage*:ti,ab,kw OR haemorrhag*:ti,ab,kw OR bleeding:ti,ab,kw OR [mh "wounds, penetrating"] OR (penetrating NEXT/1 wound*):ti,ab,kw OR (penetrating NEXT/1 injur*):ti,ab,kw OR [mh "burns"] OR burn*:ti,ab,kw 2. [mh "wounds and injuries"] 3. [mh "First Aid"] OR [mh "Community Health Workers"] OR [mh ^"Emergency Treatment"] OR [mh ^"Emergency Medical Services"] OR [mh "Emergency Service, Hospital"] OR [mh "Poison Control Centers"] OR [mh "Transportation of Patients"] OR [mh ^"Primary Health Care"] OR [mh "Acute disease"] OR [mh "emergencies"] OR [mh "self care"] OR ("acute management"):ti,ab,kw OR ("immediate care"):ti,ab,kw OR ("prehospital treatment"):ti,ab,kw OR treatment:ti,ab,kw 4. 2 AND 3 5. 1 OR 4 6. [mh "gloves, protective"] OR glove*:ti,ab,kw 7. 5-6 AND **MEDLINE** (via PubMed interface) for experimental and observational studies, guidelines and systematic reviews using the following search strategy: 1. "lacerations"[Mesh] OR "hemorrhage"[Mesh] OR laceration*[TIAB] OR hemorrhag*[TIAB] OR haemorrhag*[TIAB] OR bleeding[TIAB] OR "wounds, penetrating"[MeSH] OR penetrating wound*[TIAB] OR penetrating injur*[TIAB] OR "burns"[MeSH] OR burn*[TIAB] 2. "Wounds and Injuries"[Mesh] 3. "First Aid"[Mesh] OR "Community Health Workers"[Mesh] OR "Emergency Treatment"[Mesh:NoExp] OR "Emergency Medical Services"[Mesh:NoExp] OR "Emergency Service, Hospital"[Mesh] OR "Poison Control Centers"[Mesh] OR "Transportation of Patients"[Mesh] OR "Primary Health Care"[Mesh:NoExp] OR "Acute disease"[Mesh] OR "emergencies" [Mesh] OR "self care"[Mesh] OR "acute management" [TIAB] OR "immediate care" [TIAB] OR "prehospital treatment" [TIAB] OR treatment[TIAB] 4. 2 AND 3 5. 1 OR 4 6. "gloves, protective"[MeSH] OR glove*[TIAB] 7. 5-6 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'laceration'/exp OR 'bleeding'/exp OR laceration*:ab,ti OR hemorrhag*:ab,ti OR haemorrhag*:ab,ti OR bleeding*:ab,ti OR 'penetrating wound':ab,ti OR 'wound'/exp OR 'skin injury'/exp OR 'skin NEXT/1 injury*':ab,ti OR 'burns'/exp OR burn*:ab,ti 2. 'injury'/exp 3. 'emergency treatment'/de OR 'first aid'/exp OR 'health auxiliary'/exp OR 'emergency care'/de OR 'emergency health service'/exp OR 'poison center'/exp OR 'ambulance'/exp OR 'patient transport'/exp OR 'primary health care'/de OR 'acute disease'/exp OR 'emergency'/exp OR 'self care'/exp OR (acute NEXT/1 manag*):ab,ti OR (prehospital NEXT/1 treat*):ab,ti OR treatment:ab,ti 4. 2 AND 3 5. 1 OR 4 6. 'glove'/exp OR 'surgical glove'/exp OR glove*:ab,ti

	7. 5-6 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	24th May 2016
In/Exclusion criteria	**Population:** Include: People caring for patients with penetrating wounds, requiring surgery or requiring care in any other way involving exposure of bodily fluids. Exclude: People caring for patients requiring care that does not involve penetrating wounds, surgery or exposure of bodily fluids. **Intervention:** Include: Caregiver wearing gloves. Exclude: Caregiver wearing double gloves, triple gloves, puncture resistant gloves or gloves with puncture indicators **Comparison:** Include: Caregiver not wearing gloves. Exclude: Caregiver wearing double gloves, triple gloves, puncture resistant gloves or gloves with puncture indicators. **Outcome:** Include: Adverse effects for the caregiver. **Study design:** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: observational studies if intervention is already included in experimental studies, case series, cross-sectional studies, animal studies, ex vivo or in vitro studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English, French, German, Dutch. **Publication year**: Include: all years

Characteristics of included studies
Not available

Synthesis of findings
Not available

Quality of evidence
Not available

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	

Wound management – Wearing gloves for bleeding effects for patients (First Aid)

Question (PICO)	In people with penetrating injuries (P), does wearing gloves during treatment (I), compared to not wearing gloves (C), influence survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "lacerations"] OR [mh "hemorrhage"] OR laceration*:ti,ab,kw OR hemorrhage*:ti,ab,kw OR haemorrhag*:ti,ab,kw OR bleeding:ti,ab,kw OR [mh "wounds, penetrating"] OR (penetrating NEXT/1 wound*):ti,ab,kw OR (penetrating NEXT/1 injur*):ti,ab,kw OR [mh "burns"] OR burn*:ti,ab,kw 2. [mh "wounds and injuries"] 3. [mh "First Aid"] OR [mh "Community Health Workers"] OR [mh ^"Emergency Treatment"] OR [mh ^"Emergency Medical Services"] OR [mh "Emergency Service, Hospital"] OR [mh "Poison Control Centers"] OR [mh "Transportation of Patients"] OR [mh ^"Primary Health Care"] OR [mh "Acute disease"] OR [mh "emergencies"] OR [mh "self care"] OR ("acute management"):ti,ab,kw OR ("immediate care"):ti,ab,kw OR ("prehospital treatment"):ti,ab,kw OR treatment:ti,ab,kw 4. 2 AND 3 5. 1 OR 4 6. [mh "gloves, protective"] OR glove*:ti,ab,kw 7. 5-6 AND **MEDLINE** (via PubMed interface) for experimental and observational studies, guidelines and systematic reviews using the following search strategy: 1. "lacerations"[Mesh] OR "hemorrhage"[Mesh] OR laceration*[TIAB] OR hemorrhag*[TIAB] OR haemorrhag*[TIAB] OR bleeding[TIAB] OR "wounds, penetrating"[MeSH] OR penetrating wound*[TIAB] OR penetrating injur*[TIAB] OR "burns"[MeSH] OR burn*[TIAB] 2. "Wounds and Injuries"[Mesh] 3. "First Aid"[Mesh] OR "Community Health Workers"[Mesh] OR "Emergency Treatment"[Mesh:NoExp] OR "Emergency Medical Services"[Mesh:NoExp] OR "Emergency Service, Hospital"[Mesh] OR "Poison Control Centers"[Mesh] OR "Transportation of Patients"[Mesh] OR "Primary Health Care"[Mesh:NoExp] OR "Acute disease"[Mesh] OR "emergencies" [Mesh] OR "self care"[Mesh] OR "acute management" [TIAB] OR "immediate care" [TIAB] OR "prehospital treatment" [TIAB] OR treatment[TIAB] 4. 2 AND 3 5. 1 OR 4 6. "gloves, protective"[MeSH] OR glove*[TIAB] 7. 5-6 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'laceration'/exp OR 'bleeding'/exp OR laceration*:ab,ti OR hemorrhag*:ab,ti OR haemorrhag*:ab,ti OR bleeding*:ab,ti OR 'penetrating wound':ab,ti OR 'wound'/exp OR 'skin injury'/exp OR 'skin NEXT/1 injury*':ab,ti OR 'burns'/exp OR burn*:ab,ti 2. 'injury'/exp 3. 'emergency treatment'/de OR 'first aid'/exp OR 'health auxiliary'/exp OR 'emergency care'/de OR 'emergency health service'/exp OR 'poison center'/exp OR 'ambulance'/exp OR 'patient transport'/exp OR 'primary health care'/de OR 'acute disease'/exp OR 'emergency'/exp OR 'self care'/exp OR (acute NEXT/1 manag*):ab,ti OR (prehospital NEXT/1 treat*):ab,ti OR treatment:ab,ti 4. 2 AND 3

	5. 1 OR 4 6. 'glove'/exp OR 'surgical glove'/exp OR glove*:ab,ti 7. 5-6 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	24th May 2016
In/Exclusion criteria	**Population:** Include: Patients with penetrating wounds, requiring surgery or requiring care in any other way involving exposure of bodily fluids. Exclude: Patients requiring care that does not involve penetrating wounds, surgery or exposure of bodily fluids. **Intervention:** Include: Caregiver wearing gloves. Exclude: Caregiver wearing double gloves, triple gloves, puncture resistant gloves or gloves with puncture indicators. **Comparison:** Include: Caregiver not wearing gloves. Exclude: Caregiver wearing double gloves, triple gloves, puncture resistant gloves or gloves with puncture indicators. **Outcome:** Include: Survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of the symptoms. **Study design:** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: observational studies if intervention is already included in experimental studies, case series, cross-sectional studies, animal studies, ex vivo or in vitro studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English, French, German, Dutch. **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison/Risk factor	Remarks
Bodiwala, 1982, UK	Experimental: Randomised controlled trial	418 patients with wounds that needed to be sutured at the accident and emergency department of Leicester Royal Infirmary	Wounds sutured by qualified nurses wearing sterile gloves or no gloves	
Maitra, 1986, UK	Experimental: Randomised controlled trial	230 patients with 242 wounds, not more than 5 cm long, involving only skin and subcutaneous fat, distal to the flexor crease of the wrist (i.e. the hand), to be sutured at the accident and emergency department of the Royal Victoria Infirmary, Newcastle.	Wounds sutured by accident and emergency personnel wearing sterile gloves or no gloves.	Data were also subdivided in early vs late infections, in addition to different grades of infections. This leads to very low n-values (n=0-7), therefore data from these analyses were not extracted.

Synthesis of findings

Outcome	Comparison/Risk factor	Effect Size	#studies, # participants	Reference
Infection rate	Gloves vs no gloves	Not statistically significant: 35/202 vs 26/206 § RR: 1.37, 95%CI [0.86;2.19] * ¥ (p=0.19)	1, 202 vs 206	Bodiwala, 1982
		Not statistically significant: 18/121 vs 17/121 § RR: 1.06, 95%CI [0.57;1.95] * ¥ (p=0.86)	1, 121 vs 121	Maitra, 1986
Mild infection rate (redness and/or serous discharge present)		Not statistically significant: 27/202 vs 27/206 § RR: 1.02, 95%CI [0.62;1.68] * ¥ (p=0.94)	1, 202 vs 206	Bodiwala, 1982
Severe infection rate (pus and/or wound dehiscence)		Not statistically significant: 8/202 vs 9/206 § RR: 0.91, 95%CI [0.36;2.30] * ¥ (p=0.84)		
Grade I infection rate (erythema not more than 1 cm from suture line		Not statistically significant: 12/121 vs 9/121 § RR:1.33, 95%CI [0.58;3.05] * ¥ (p=0.50)	1, 121 vs 121	Maitra, 1986
Grade II infection rate (erythema > 1 cm from suture line with oedema)		Not statistically significant: 5/121 vs 2/121 § RR: 2.50, 95%CI [0.49;12.64] * ¥ (p=0.27)		
Grade III infection rate (pus present, together with Grade I or II)		Not statistically significant: 1/121 vs 6/121 § RR: 0.17, 95%CI [0.02;1.36] * ¥ (p=0.09)		
Early infection rate (< 48h after suture)		Not statistically significant: 9/121 vs 10/121 § RR: 0.90, 95%CI [0.38;2.14] * ¥ (p=0.81)		
Late infection rate (>8 days after suture)		Not statistically significant: 9/121 vs 8/121 § RR: 1.13, 95%CI [0.45;2.82] * ¥ (p=0.80)		

* Calculations done by the reviewer(s) using Review Manager software

¥ Imprecision (large variability of results)

§ Imprecision (low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Bodiwala, 1982	Yes, forms with instructions were mixed randomly, but nurses could "pick out a form"	No, outcome assessors were blinded to the treatment procedure	No, loss to follow up was accounted for	Yes, time to healing was not reported	Unclear whether other factors, which were shown to influence the infection rate (e.g. location of wound) were properly randomised between treatments. No information reported about timing of wound inspection. Inspection was performed by others (general practioner/nurse) for a subgroup of patients that did not return to the hospital for inspection.
Maitra, 1986,	Yes, senior house officers "picked" randomly ordered cards in sequence	No, outcome assessors were blinded to the treatment procedure	No, no loss to follow up	Yes, time to healing was not reported	No information about timing of wound inspection.

Level of the body of evidence

	High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Low numbers of events and large variability of the results
Inconsistency	0	
Indirectness	-1	Hospital setting
Publication bias	0	
QUALITY (GRADE)	**Very Low [D]**	

Conclusion	There is limited evidence neither in favour of wearing sterile gloves nor not wearing gloves: A statistically significant decrease of wound infections in the injured victim, when wearing sterile gloves compared to not wearing gloves during wound suture, could not be demonstrated (Bodiwala 1982, Maitra 1986). Evidence is of very low quality and results of these studies are imprecise due to low numbers of events and large variability of results.
Reference(s)	**Articles** Bodiwala GG, George TK. *Surgical gloves during wound repair in the accident-and-emergency department.* Lancet. 1982, 2(8289):91-2. Maitra AK, Adams JC. *Use of sterile gloves in the management of sutured hand wounds in the A&E department.* Injury. 1986, 17(3):193-5.

Wound management – Wearing plastic bags for bleeding for care givers (First Aid)

Question (PICO)	In people treating people with penetrating injuries (P), does wearing plastic bags during treatment (I), compared to not wearing plastic bags or wearing gloves (C), influence the rate of infection (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "lacerations"] OR [mh "hemorrhage"] OR laceration*:ti,ab,kw OR hemorrhage*:ti,ab,kw OR haemorrhag*:ti,ab,kw OR bleeding:ti,ab,kw OR [mh "wounds, penetrating"] OR (penetrating NEXT/1 wound*):ti,ab,kw OR (penetrating NEXT/1 injur*):ti,ab,kw OR [mh "burns"] OR burn*:ti,ab,kw 2. [mh "wounds and injuries"] 3. [mh "First Aid"] OR [mh "Community Health Workers"] OR [mh ^"Emergency Treatment"] OR [mh ^"Emergency Medical Services"] OR [mh "Emergency Service, Hospital"] OR [mh "Poison Control Centers"] OR [mh "Transportation of Patients"] OR [mh ^"Primary Health Care"] OR [mh "Acute disease"] OR [mh "emergencies"] OR [mh "self care"] OR ("acute management"):ti,ab,kw OR ("immediate care"):ti,ab,kw OR ("prehospital treatment"):ti,ab,kw OR treatment:ti,ab,kw 4. 2 AND 3 5. 1 OR 4 6. ([mh "plastics"] AND bag*:ti,ab,kw) OR (plastic*:ti,ab,kw AND bag*:ti,ab,kw) OR ([mh "plastics"] AND barrier*:ti,ab,kw) OR (plastic*:ti,ab,kw AND barrier*:ti,ab,kw) OR ([mh "plastics"] AND foil*:ti,ab,kw) OR (plastic*:ti,ab,kw AND foil*:ti,ab,kw) OR ([mh "plastics"] AND wrap*:ti,ab,kw) OR (plastic*:ti,ab,kw AND foil*:ti,ab,kw) 7. 5-6 AND **MEDLINE** (via PubMed interface) for experimental and observational studies, guidelines and systematic reviews using the following search strategy: 1. "lacerations"[Mesh] OR "hemorrhage"[Mesh] OR laceration*[TIAB] OR hemorrhag*[TIAB] OR haemorrhag*[TIAB] OR bleeding[TIAB] OR "wounds, penetrating"[MeSH] OR penetrating wound*[TIAB] OR penetrating injur*[TIAB] OR "burns"[MeSH] OR burn*[TIAB] 2. "Wounds and Injuries"[Mesh] 3. "First Aid"[Mesh] OR "Community Health Workers"[Mesh] OR "Emergency Treatment"[Mesh:NoExp] OR "Emergency Medical Services"[Mesh:NoExp] OR "Emergency Service, Hospital"[Mesh] OR "Poison Control Centers"[Mesh] OR "Transportation of Patients"[Mesh] OR "Primary Health Care"[Mesh:NoExp] OR "Acute disease"[Mesh] OR "emergencies" [Mesh] OR "self care"[Mesh] OR "acute management" [TIAB] OR "immediate care" [TIAB] OR "prehospital treatment" [TIAB] OR treatment[TIAB] 4. 2 AND 3 5. 1 OR 4 6. ("plastics"[MeSH] AND bag*[TIAB]) OR (plastic*[TIAB] AND bag*[TIAB]) OR ("plastics"[MeSH] AND barrier*[TIAB]) OR (plastic*[TIAB] AND barrier*[TIAB]) OR ("plastics"[MeSH] AND foil*[TIAB]) OR (plastic*[TIAB] AND foil*[TIAB]) OR ("plastics"[MeSH] AND wrap*[TIAB]) OR (plastic*[TIAB] AND foil*[TIAB]) 7. 5-6 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'laceration'/exp OR 'bleeding'/exp OR laceration*:ab,ti OR hemorrhag*:ab,ti OR haemorrhag*:ab,ti OR bleeding*:ab,ti OR 'penetrating wound':ab,ti OR 'wound'/exp OR 'skin injury'/exp OR 'skin NEXT/1 injury*':ab,ti OR 'burns'/exp OR burn*:ab,ti 2. 'injury'/exp 3. 'emergency treatment'/de OR 'first aid'/exp OR 'health auxiliary'/exp OR 'emergency care'/de OR 'emergency health service'/exp OR 'poison center'/exp OR 'ambulance'/exp OR

	'patient transport'/exp OR 'primary health care'/de OR 'acute disease'/exp OR 'emergency'/exp OR 'self care'/exp OR (acute NEXT/1 manag*):ab,ti OR (prehospital NEXT/1 treat*):ab,ti OR treatment:ab,ti 4. 2 AND 3 5. 1 OR 4 6. ('plastic'/exp AND bag*:ab,ti) OR (plastic*:ab,ti AND bag*:ab,ti) OR ('plastic'/exp AND barrier*:ab,ti) OR (plastic*:ab,ti AND barrier*:ab,ti) OR ('plastic'/exp AND foil*:ab,ti) OR (plastic*:ab,ti AND foil*:ab,ti) OR ('plastic'/exp AND wrap*:ab,ti) OR (plastic*:ab,ti AND foil*:ab,ti) 7. 5-6 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	30th May 2016
In/Exclusion criteria	**Population:** Include: People caring for patients with penetrating wounds, requiring surgery or requiring care in any other way involving exposure of bodily fluids. Exclude: People caring for patients requiring care that does not involve penetrating wounds, surgery or exposure of bodily fluids. **Intervention:** Include: Caregiver wearing plastic bags. **Comparison:** Include: Caregiver not wearing plastic bags, caregiver wearing gloves. **Outcome:** Include: Adverse effects for the caregiver. **Study design:** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: observational studies if intervention is already included in experimental studies, case series, cross-sectional studies, animal studies, ex vivo or in vitro studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English, French, German, Dutch. **Publication year**: Include: all years

Characteristics of included studies
Not available

Synthesis of findings
Not available

Quality of evidence
Not available

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	

Wound management – Wearing plastic bags for bleeding for patients (First Aid)

Question (PICO)	In people with penetrating injuries (P), does wearing plastic bags during treatment (I), compared to not wearing plastic bags or wearing gloves (C), influence survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "lacerations"] OR [mh "hemorrhage"] OR laceration*:ti,ab,kw OR hemorrhage*:ti,ab,kw OR haemorrhag*:ti,ab,kw OR bleeding:ti,ab,kw OR [mh "wounds, penetrating"] OR (penetrating NEXT/1 wound*):ti,ab,kw OR (penetrating NEXT/1 injur*):ti,ab,kw OR [mh "burns"] OR burn*:ti,ab,kw 2. [mh "wounds and injuries"] 3. [mh "First Aid"] OR [mh "Community Health Workers"] OR [mh ^"Emergency Treatment"] OR [mh ^"Emergency Medical Services"] OR [mh "Emergency Service, Hospital"] OR [mh "Poison Control Centers"] OR [mh "Transportation of Patients"] OR [mh ^"Primary Health Care"] OR [mh "Acute disease"] OR [mh "emergencies"] OR [mh "self care"] OR ("acute management"):ti,ab,kw OR ("immediate care"):ti,ab,kw OR ("prehospital treatment"):ti,ab,kw OR treatment:ti,ab,kw 4. 2 AND 3 5. 1 OR 4 6. ([mh "plastics"] AND bag*:ti,ab,kw) OR (plastic*:ti,ab,kw AND bag*:ti,ab,kw) OR ([mh "plastics"] AND barrier*:ti,ab,kw) OR (plastic*:ti,ab,kw AND barrier*:ti,ab,kw) OR ([mh "plastics"] AND foil*:ti,ab,kw) OR (plastic*:ti,ab,kw AND foil*:ti,ab,kw) OR ([mh "plastics"] AND wrap*:ti,ab,kw) OR (plastic*:ti,ab,kw AND foil*:ti,ab,kw) 7. 5-6 AND **MEDLINE** (via PubMed interface) for experimental and observational studies, guidelines and systematic reviews using the following search strategy: 1. "lacerations"[Mesh] OR "hemorrhage"[Mesh] OR laceration*[TIAB] OR hemorrhag*[TIAB] OR haemorrhag*[TIAB] OR bleeding[TIAB] OR "wounds, penetrating"[MeSH] OR penetrating wound*[TIAB] OR penetrating injur*[TIAB] OR "burns"[MeSH] OR burn*[TIAB] 2. "Wounds and Injuries"[Mesh] 3. "First Aid"[Mesh] OR "Community Health Workers"[Mesh] OR "Emergency Treatment"[Mesh:NoExp] OR "Emergency Medical Services"[Mesh:NoExp] OR "Emergency Service, Hospital"[Mesh] OR "Poison Control Centers"[Mesh] OR "Transportation of Patients"[Mesh] OR "Primary Health Care"[Mesh:NoExp] OR "Acute disease"[Mesh] OR "emergencies" [Mesh] OR "self care"[Mesh] OR "acute management" [TIAB] OR "immediate care" [TIAB] OR "prehospital treatment" [TIAB] OR treatment[TIAB] 4. 2 AND 3 5. 1 OR 4 6. ("plastics"[MeSH] AND bag*[TIAB]) OR (plastic*[TIAB] AND bag*[TIAB]) OR ("plastics"[MeSH] AND barrier*[TIAB]) OR (plastic*[TIAB] AND barrier*[TIAB]) OR ("plastics"[MeSH] AND foil*[TIAB]) OR (plastic*[TIAB] AND foil*[TIAB]) OR ("plastics"[MeSH] AND wrap*[TIAB]) OR (plastic*[TIAB] AND foil*[TIAB]) 7. 5-6 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'laceration'/exp OR 'bleeding'/exp OR laceration*:ab,ti OR hemorrhag*:ab,ti OR haemorrhag*:ab,ti OR bleeding*:ab,ti OR 'penetrating wound':ab,ti OR 'wound'/exp OR 'skin injury'/exp OR 'skin NEXT/1 injury*':ab,ti OR 'burns'/exp OR burn*:ab,ti 2. 'injury'/exp

	3. 'emergency treatment'/de OR 'first aid'/exp OR 'health auxiliary'/exp OR 'emergency care'/de OR 'emergency health service'/exp OR 'poison center'/exp OR 'ambulance'/exp OR 'patient transport'/exp OR 'primary health care'/de OR 'acute disease'/exp OR 'emergency'/exp OR 'self care'/exp OR (acute NEXT/1 manag*):ab,ti OR (prehospital NEXT/1 treat*):ab,ti OR treatment:ab,ti 4. 2 AND 3 5. 1 OR 4 6. ('plastic'/exp AND bag*:ab,ti) OR (plastic*:ab,ti AND bag*:ab,ti) OR ('plastic'/exp AND barrier*:ab,ti) OR (plastic*:ab,ti AND barrier*:ab,ti) OR ('plastic'/exp AND foil*:ab,ti) OR (plastic*:ab,ti AND foil*:ab,ti) OR ('plastic'/exp AND wrap*:ab,ti) OR (plastic*:ab,ti AND foil*:ab,ti) 7. 5-6 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	30th May 2016
In/Exclusion criteria	**Population:** Include: Patients with penetrating wounds, requiring surgery or requiring care in any other way involving exposure of bodily fluids. Exclude: Patients requiring care that does not involve penetrating wounds, surgery or exposure of bodily fluids. **Intervention:** Include: Caregiver wearing plastic bags. **Comparison:** Include: Caregiver not wearing plastic bags, caregiver wearing gloves. **Outcome:** Include: Survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of the symptoms. **Study design:** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: observational studies if intervention is already included in experimental studies, case series, cross-sectional studies, animal studies, ex vivo or in vitro studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English, French, German, Dutch. **Publication year**: Include: all years

Characteristics of included studies
Not available

Synthesis of findings
Not available

Quality of evidence
Not available

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	

Trauma - Keeping warm (First Aid)

Question (PICO)	In humans with severe bleeding/trauma (P) is not keeping the victim warm (RF) a risk factor for increased blood loss, complications or mortality (O) compared to keeping the victim warm (C)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the search terms: 1. [mh "Abdominal injuries"] or [mh "Multiple Trauma"] or [mh "Shock, Traumatic"] or [mh "Thoracic Injuries"] or [mh "Wounds, Nonpenetrating"] or [mh "Wounds, Penetrating"] or [mh Lacerations] or [mh "Vascular System Injuries"] or (trauma):ti,ab,kw or (traumatic NEXT injur*):ti,ab,kw or (bleeding):ti,ab,kw 2. hot:ti,ab,kw or warm:ti,ab,kw or Heat:ti,ab,kw or hot:ti,ab,kw or warm:ti,ab,kw or [mh "hypothermia"] or Hypothermia:ti,ab,kw or (body NEXT temperature):ti,ab,kw OR thermostasis:ti,ab,kw OR thermogenesis:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for guidelines, systematic reviews or experimental studies using the following search strategy: 1. "Hemorrhage"[Mesh] OR hemoorhage*[TIAB] OR bleeding[TIAB] OR Trauma[TIAB] OR traumatic injur*[TIAB] OR "lacerations"[Mesh] OR "wounds,nonpenetrating"[Mesh] OR laceration*[TIAB] OR "nonpenetrating wound"[TIAB] OR "nonpenetrating wounds"[TIAB] OR "nonpenetrating injury"[TIAB] OR "nonpenetrating injuries"[TIAB] OR "blunt injury"[TIAB] OR "blunt injuries"[TIAB] 2. Heat*[TIAB] OR hot[TIAB] OR warm*[TIAB] OR "Hot Temperature/therapeutic use"[Mesh] Or "Rewarming" [Mesh] OR "Hypothermia"[Mesh] OR Hypothermia[TIAB] OR "body temperature"[TIAB] OR thermostasis[TIAB] OR thermogenesis[TIAB] 3. "First Aid"[Mesh] OR "Community Health Workers"[Mesh] OR "Emergency Treatment"[Mesh:NoExp] OR "Emergency Medical Services"[Mesh:NoExp] OR "Emergency Service, Hospital"[Mesh] OR "Poison Control Centers"[Mesh] OR "Transportation of Patients"[Mesh] OR "Primary Health Care"[Mesh:NoExp] OR "Acute disease"[Mesh] OR "emergencies" [Mesh] OR "self care"[Mesh] OR "acute management" [TIAB] OR "immediate care" [TIAB] OR "prehospital treatment" [TIAB] OR "first aid"[TIAB] OR "self care"[TIAB] OR emergenc*[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) for systematic reviews or experimental studies using the following search strategy: 1. 'penetrating trauma'/exp OR 'laceration'/exp OR 'blunt trauma'/exp OR 'bleeding'/exp OR laceration*:ab,ti OR 'nonpenetrating wound':ab,ti OR 'nonpenetrating wounds':ab,ti OR 'nonpenetrating injury':ab,ti OR 'nonpenetrating injuries':ab,ti OR 'blunt injury':ab,ti OR 'blunt injuries':ab,ti OR hemorrhage*:ab,ti OR bleeding*:ab,ti OR 'bleeding'/exp OR Trauma:ab,ti OR (traumatic NEXT/1 injur*):ab,ti 2. Heat*:ab,ti OR hot:ab,ti OR warm*:ab,ti OR 'heat'/exp OR 'hypothermia'/exp OR hypothermia:ab,ti OR 'body temperature': ab,ti OR thermostasis:ab,ti OR thermogenesis:ab,ti 3. 'first aid'/exp OR 'health auxiliary'/exp OR 'emergency treatment'/de OR 'emergency health service'/exp OR 'poison center'/exp OR 'patient transport'/exp OR 'primary health care'/exp OR 'acute disease'/exp OR 'emergency'/exp OR 'self care'/exp OR 'acute management':ab,ti OR 'immediate care':ab,ti OR 'prehospital treatment':ab,ti OR 'self care':ab,ti OR 'first aid':ab,ti OR emergenc*:ab,ti Selected articles were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	12-03-2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages.

	Intervention: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: Primary outcomes: mortality, blood loss, complications such as organ failure, respiratory syndromes, shock, coma, inflammation, sepsis, cardiac arrest. Exclude: Secondary outcomes: days in hospital, duration of ventilation; measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies. **Language**: Include: English **Publication year**: Include: all years

Characteristics of included studies

Author, Year, Country	Study design	Population	Comparison	Remarks
Arthurs, 2006, USA	Observational: Cross-sectional study	2848 patients (2762 males, 86 females), mean age 28±10 years, with an initial temperature recording on arrival at Combat Surgical Hospital between January 2004 and December 2004. 82% was normothermic (n=2335), 16% was mildly hypothermic (n=455), 2% was moderately (n=57) and 0.2% severly hypothermic (n=5)	1. Mild hypothermia: T=34-36°C 2. Moderate-severe hypothermia: T<34°C 3. Normothermia: T>36°C	
Beilman, 2009, USA	Observational: cross-sectional study	383 adult patients (279 male, 104 female), mean age 39±17 years, from 7 level I trauma centers, who were admitted to emergency department (between October 2004 and February 2006) within 6 hours of injury and had packed red blood cells transfused in the field or within 6 hours of arrival to ED. 155 had hypothermia, 204 had no hypothermia	- Hypothermia: T<35°C - No hypothermia: T≥35°C	
Bukur, 2012, USA	Observational: cross-sectional study	21023 patients (15389 male, 5634 female), mean age 39.9±19.5 years, in the Los Angeles County Trauma	- Hypothermia: T<36.5 - Normothermic: T≥36.5	

		System Database (data between 2005-2009) with available temperature, transfusion and outcome data available. 11642 had hypothermia, 9381 had normal temperatures.		
Ireland, 2011, Australia	Observational: cross-sectional study	732 patients (556 male, 176 female), mean age 45.8±20.6 years, with major trauma (mean Injury Severity Score (ISS) of 22), identified from Alfred Health's trauma registry of which 97 were hypothermic and 584 had normal temperature.	- Hypothermia: T<35°C - Normothermia: 35°C≤T≤37.5°C	
Martin, 2005, USA	Observational: cross-sectional study	700,304 patients extracted from the National Trauma Data Bank with an admission temperature recorded of which 11,026 had hypothermia (mean age 39.4±22.4; 7580 male/3446 female) and 689,278 had normal temperatures (mean age 37.8±22.9; 451,596 male/237,682 female)	- Hypothermia: T<35°C - Normothermia: T≥35°C	
Mommsen, 2013, Germany	Observational: Cross-sectional study	310 patients, mean age 41.9±17.5 (220 male, 90 female), with multiple injuries (ISS≥16) who were treated at the level 1 Trauma centre between January 2005 and March 2009. 114 patients had hypothermia, 196 patients had normal temperatures	- Hypothermia: T<35°C - Normothermia: T≥35°C	
Seekamp, 1995, Germany	Observational: cross-sectional study	641 trauma patients with ISS >25 who were admitted between 1988 and 1993. 400 patients had a T≥34°C, 226 patients had a T<34°C	- Hypothermia: T<34°C - Normothermia: T≥34°C	
Shafi, 2005, USA	Observational: Cross-sectional study	38,550 patients from the National Trauma Databank (study period: 1994-2002), mean age 34±10 years (29265 men, 9285 women)	- Hypothermia: T<35°C - Normothermia: T≥35°C	
Sundberg, 2011, USA	Observational: cross-sectional study	190 pediatric trauma patients (<17 years, 118 male/72 female) who presented to the pediatric emergency department of a tertiary, urban level 1 children's trauma center between September 2006 and March 2008.	- Hypothermia: T<35°C - Normothermia: T≥35°C	
Thompson, 2010, USA	Observational: cross-sectional study	147 patients admitted to a level I trauma center following severe traumatic brain injury from January 2000 to January	- Hypothermia: T<35°C - Normothermia: T≥35°C	

		2002. Mean age of hypothermic patients (n=59) was 34.9±2.3 years; mean age of normothermic patients (n=88) was 37.5±2.0 years.		
Waibel, 2010, USA	Observational: cross-sectional study	1629 patients admitted to the rural level I trauma center between July 2002 and June 2007 with injury. 182 patients were hypothermic, 1447 were normothermic.	- Hypothermia: T<36°C - Normothermia: T≥36°C	
Wang, 2005	Observational: cross-sectional study	Data of 38520 trauma patients between January 2000 and December 2002 extracted from the Pennsylvania Trauma Outcome Study. 1921 patients had a temperature ≤35°C (1353 males, 568 females) and 36599 patients had normal temperature (22519 males, 14080 females)	- Hypothermia: T≤35°C - Normothermia: T>35°C	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Mortality				
Mortality	Hypothermia (T<36°C) vs normothermia	Statistically significant: 45/509 vs 46/2334 OR: 4.82, 95%CI [3.16; 7.36] (P<0.00001)* *In favour of normothermia*	1, 509 vs 2334	Arthurs, 2006
	Hypothermia (T<35°C) vs no hypothermia	Not statistically significant: 25/152 vs 25/204 £ (p=0.2826)	1, 152 vs 204 §	Beilman, 2009
	Hypothermia (T<36.5°C) vs no hypothermia	Statistically significant: 516/9381 vs 396/11642 OR: 1.3, 95%CI [1.2; 1.4] (p<0.001) *In favour of no hypothermia*	1, 9381 vs 11642	Bukur, 2012
	Hypothermia (T<35°C) vs no hypothermia	Statistically significant: 29/97 vs 35/584 OR: 6.7, 95%CI [3.87; 11.55] (p<0.001) *In favour of no hypothermia*	1, 97 vs 584 §	Ireland, 2011
		Statistically significant: 2812/11026 vs 20678/689278 £ p<0.001 *In favour of no hypothermia*	1, 11026 vs 689278	Martin, 2005
		Statistically significant: 16/114 vs 11/196 £ (p=0.020) *In favour of no hypothermia*	1, 114 vs 196 §	Mommsen, 2013
	Hypothermia (T<34°C) vs no hypothermia	Statistically significant: 109/226 vs 114/400 OR: 2.34, 95%CI [1.66; 3.28] (p<0.00001)* *In favour of no hypothermia*	1, 226 vs 400 §	Seekamp, 1995
		Statistically significant:	1, 3267 vs 35283	Shafi, 2005

	Hypothermia (T<35°C) vs no hypothermia	OR: 1.19, 95%CI [1.05; 1.35], p=0.008 *In favour of no hypothermia*		
		Statistically significant: Adjusted for seasonal variation: OR: 9.2, 95%CI [3.2; 26.2], (p<0.0001) *In favour of no hypothermia* Adjusted for mode of transportation (ground vs air): OR: 8.7, 95%CI [3.1; 24.6], (p<0.0001) *In favour of no hypothermia*	1, 22 vs 168 §	Sundberg, 2011
	Hypothermia (T<36°C) vs no hypothermia	Statistically significant: aOR: 2.41, 95%CI [1.12; 5.22], (p=0.025) *In favour of no hypothermia*	1, 182 vs 1447	Waibel, 2010
	Hypothermia (T≤35°C) vs no hypothermia	Statistically significant: OR: 3.03, 95%CI [2.62; 3.51], (p<0.00001) *In favour of no hypothermia*	1, 36599 vs 1921	Wang, 2005
Blood loss				
Estimated blood loss (mL)	Mild hypothermia vs normothermia	Statistically significant: 806±1206 vs 370±910 MD: 436.0, 95%CI [319.20; 552.80] (p<0.00001)* *In favour of normothermia*	1, 455 vs 2335	Arthurs, 2006
	Moderate-severe hypothermia vs normothermia	Statistically significant: 1317±2581 vs 370±910 MD: 947.0, 95%CI [303.49; 1590.51] (p<0.004)* *In favour of normothermia*	1, 62 vs 2335	
Total transfusion volume (mL)	Hypothermia (T<36.5°C) vs no hypothermia	Statistically significant: 935.7±3110 vs 562.7±2200 MD: 373.00, 95%CI [301.0; 444.9] (p<0.001) *In favour of no hypothermia*	1, 9381 vs 11642	Bukur, 2012
Transfusion of packed red blood cells (units)	Mild hypothermia vs normothermia	Statistically significant: 6.5±5 vs 4.8±5 MD: 1.7, 95%CI [1.19, 2.21] (p<0.00001)* *In favour of normothermia*	1, 455 vs 2335	Arthurs, 2006
	Moderate-severe hypothermia vs normothermia	Statistically significant: 9.6±9 vs 4.8±5 MD: 4.80, 95%CI [2.55, 7.05] (p<0.0001)* *In favour of normothermia*	1, 62 vs 2335	
	Hypothermia (T<35°C) vs no hypothermia	Not statistically significant: OR: 1.05, 95%CI [0.99; 1.10] (p=0.088)	1, 69 vs 49	Ireland, 2011
		Statistically significant: 18.2±19.2 vs 11.5±14.5 MD: 6.70 (p=0.005) £ *In favour of no hypothermia*	1, 114 vs 196 §	Mommsen, 2013
Transfusion of packed red blood cells (mL)		Statistically significant: 3281±4242 vs 1543±2094 MD: 1738.0 (p<0.0001) £ *In favour of no hypothermia*	1, 155 vs 204	Beilman, 2009

Transfusion of fresh frozen plasma (units)	Mild hypothermia vs normothermia	Statistically significant: 5.5±4 vs 4.9±5 MD: 0.60, 95%CI [0.18, 1.02] (p<0.005)* *In favour of normothermia*	1, 455 vs 2335	Arthurs, 2006
	Hypothermia (T<35°C) vs no hypothermia	Statistically significant: 12.5±14.1 vs 7.6±11.5 MD: 4.90 (p<0.001)£ *In favour of no hypothermia*	1, 114 vs 196 §	Mommsen, 2013
		Not statistically significant: OR: 1.00, 95%CI [0.99; 1.00] (p=0.135)	1, 44 vs 39	Ireland, 2011
Transfusion of platelets (units)		Statistically significant: 2.1±3.4 vs 1.1±3.6 MD: 1.00 (p<0.001) £ *In favour of no hypothermia*	1, 114 vs 196 §	Mommsen, 2013
		Not statistically significant: OR: 0.95, 95%CI [0.82; 1.11] (p=0.531)	1, 25 vs 22	Ireland, 2011
Complications				
Shock (SBP < 90 mmHg)	Hypothermia (<36°C) vs no hypothermia	Statistically significant: OR: 5.7, 95%CI [4.0, 8.0] (p<0.01) *In favour of no hypothermia*	1, 517 vs 2335	Arthurs, 2006
	Hypothermia (<36.5°C) vs no hypothermia	Statistically significant: 460/9335 vs 273/11622 (p<0.001) £ *In favour of no hypothermia*	1, 9335 vs 11622	Bukur, 2012
	Hypothermia (T<36°C) vs no hypothermia	Statistically significant: 21/182 vs 46/1447 (p<0.001) £ *In favour of no hypothermia*	1, 182 vs 1447	Waibel, 2010
Glasgow Coma Scale	1. Mild hypothermia 2. Moderate-severe hypothermia 3. Normothermia	Statistically significant: Mild hypothermia vs normothermic: 12.6±4.4 vs 13.9±3.1 MD: -1.30, 95%CI [-1.72, -0.88] (p<0.00001)* *In favour of normothermia*	1, 455 vs 2335	Arthurs, 2006
		Statistically significant: Moderate-severe hypothermia vs normothermic: 7.7±5.6 vs 13.9±3.1 MD: - 6.20, 95%CI [-7.60, -4.80] (p<0.00001)* *In favour of normothermia*	1, 62 vs 2335	
	Hypothermia (T<35°C) vs no hypothermia	Statistically significant: 10.8 vs 14.2 MD: -3.4 £ (p<0.001) *In favour of no hypothermia*	1, 11026 vs 689278	Martin, 2005
		Statistically significant: 6.3±0.4 vs 7.8±0.3 MD: -1.50 £ (p<0.01) *In favour of no hypothermia*	1, 59 vs 88 §	Thompson, 2010
	Hypothermia (T<36°C) vs no hypothermia	Statistically significant: (9.3 vs 13.2)	1, 182 vs 1447	Waibel, 2010

		MD: -3.9, p<0.001 £ *In favour of no hypothermia*		
Glasgow Coma Scale ≤8		Statistically significant: OR: 3.4, 95%CI [2.6; 4.3] (p<0.01) *In favour of no hypothermia*	1, 517 vs 2335	Arthurs, 2006
	Hypothermia (<36.5°C) vs no hypothermia	Statistically significant: 770/9256 vs 688/11480 (p<0.001) £ *In favour of no hypothermia*	1, 9256 vs 11480	Bukur, 2012
	Hypothermia (T<35°C) vs no hypothermia	Statistically significant: 21/22 vs 63/168 OR: 35.00, 95%CI [4.60; 266.56] (p=0.0006)* *In favour of no hypothermia*	22 vs 168	Sundberg, 2011
Multiple Organ Dysfunction Syndrome (MODS)		Statistically significant: 28/134 vs 17/187 OR: 2.64, 95%CI [1.38; 5.06] (p=0.003)* *In favour of no hypothermia*	1, 134 vs 187 §	Beilman, 2009
		Not statistically significant: 16/114 vs 13/196 (P=0.486) £	1, 114 vs 196 §	Mommsen, 2013
Adult Respiratory Distress Syndrome (ARDS)	Hypothermia (<36.5°C) vs no hypothermia	Statistically significant: 236/9381 vs 178/11642 OR: 1.3, 95%CI [1.2; 1.5] (p<0.001) *In favour of no hypothermia*	1, 9381 vs 11642	Bukur, 2012
	Hypothermia (T<35°C) vs no hypothermia	Statistically significant: 111/3267 vs 529/35283 OR: 2.31, 95%CI [1.88; 2.84] (p<0.00001)* *In favour of no hypothermia*	1, 3267 vs 35283	Shafi, 2005
	Hypothermia (T<36°C) vs no hypothermia	Not statistically significant: 2/182 vs 9/1447 (p=0.353) £	1, 182 vs 1447	Waibel, 2010
Pneumonia	Hypothermia (<36.5°C) vs no hypothermia	Statistically significant: 388/9381 vs 334/11642 OR: 1.5, 95%CI [1.3; 1.7] (p<0.001) *In favour of no hypothermia*	1, 9381 vs 11642	Bukur, 2012
	Hypothermia (T<35°C) vs no hypothermia	Statistically significant: 392/3267 vs 1764/35283 OR: 2.59, 95%CI [2.31; 2.91] (p<0.00001)* *In favour of no hypothermia*	1, 3267 vs 35283	Shafi, 2005
Respiratory failure	Hypothermia (T<36°C) vs no hypothermia	Statistically significant: 28/182 vs 84/1447 (p<0.001) £ *In favour of no hypothermia*	1, 182 vs 1447	Waibel, 2010
Systemic Inflammatory Response Syndrome (SIRS)	Hypothermia (T<35°C) vs no hypothermia	Not statistically significant: 96/114 vs 144/196 (p=0.091) £	1, 114 vs 196 §	Mommsen, 2013
Sepsis		Not statistically significant: 56/114 vs 77/196 (p=0.188) £		

Infections		Statistically significant: 490/3267 vs 2470/35283 OR: 2.34, 95%CI [2.11; 2.60] (p<0.00001)* *In favour of no hypothermia*	1, 3267 vs 35283	Shafi, 2005
Any complications		Statistically significant: 817/3267 vs 3881/35283 OR: 2.70, 95%CI [2.48; 2.94] (P<0.00001)* *In favour of no hypothermia*		
Cardiac arrest		Statistically significant: 49/3267 vs 141/35283 OR: 3.80, 95%CI [2.74; 5.26] (P<0.00001)* *In favour of no hypothermia*		
Number of complications during hospitalization		Statistically significant: 2.3±0.2 vs 1.3±0.2 MD: 1.00, 95%CI [0.93; 1.07] (P<0.00001)* *In favour of no hypothermia*	1, 59 vs 88 §	Thompson, 2010

Mean ± SD (unless otherwise indicated)

* Calculations done by the reviewer(s) using Review Manager software

§ Imprecision (limited sample size)

£ No CI calculated because unable to adjust for confounding factors

Quality of evidence:

Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations
Arthurs, 2006	No	No	Yes, no data on time of year, time of injury, time for extrication and time to evacuation	No	
Beilman, 2009	No	No	No	No	
Bukur, 2012	Yes, differences in age, % penetrating injury	No	Unclear	No	Causation cannot be definitively established, prehospital scene and transport time were not analyzed,…
Ireland, 2011	No	No	No, confounders are well described and accounted in calculations	No	
Martin, 2005	Yes, differences in age, gender, % penetrating injury	No	Unclear, "while corrected for confounders" but not stated	No	

			which confoundes		
Mommsen, 2013	No	No	No, confounders are described and accounted in calculations	No	
Seekamp, 1995	Unclear, demographic data of groups not mentioned	No	Unclear, not mentioned	No	
Shafi, 2005	No, no differences in age or gender	No	Unclear, not mentioned	No	
Sundberg, 2011	Yes, differences in age, but no differences in gender	No	No, they accounted for seaon and mode of transportation	No	
Thompson, 2010	No, no differences in age or gender	No	Unclear	No	
Waibel, 2010	No, no differences in age or gender	No	Unclear	No	
Wang, 2005	No, differences in gender	No	No, adjusted for age, ISS, injuries, blood pressure and temperature measurement route	No	

Leve of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	0	[low number of events]
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Conclusion(s)	There is limited evidence from 12 observational studies with harm for hypothermia. (In making this evidence conclusion, we place a higher value over the significant outcomes of larger studies) **Mortality** It was shown that hypothermia resulted in a statistically significant increased risk of death, compared to no hypothermia (Arthurs 2006, Beilman 2009, Bukur 2012, Ireland 2011, Martin 2005, Mommsen 2013, Seekamp 1995, Shafi 2005, Sundberg, Waibel 2010, Wang 2005). **Blood loss** It was shown that hypothermia resulted in a statistically significant increased risk of blood loss, total transfusion volume, transfusion of packed red blood cells, transfusion of fresh frozen plasma and transfusion of platelets, compared to no hypothermia (Arthurs 2006, Beilman 2009, Bukur 2012, Ireland 2011, Martin 2005, Mommsen 2013, Seekamp 1995, Shafi 2005, Sundberg, Waibel 2010, Wang 2005). **Complications** It was shown that hypothermia resulted in a statistically significant increased risk of complications, such as shock, coma, multiple organ disfunction syndrome, ARDS,

	pneumonia, respiratory failure, SIRS, sepsis, infections and cardiac arrest, compared to no hypothermia (Arthurs 2006, Beilman 2009, Bukur 2012, Ireland 2011, Martin 2005, Mommsen 2013, Seekamp 1995, Shafi 2005, Sundberg, Thompson, Waibel 2010, Wang 2005). Evidence is of very low quality.
Reference(s)	**Articles:** Arthurs Z, Cuadrado D, Beekley A, Grathwohl K, Perkins J, Rush R, Sebesta J. *The impact of hypothermia on trauma care at the 31st combat support hospital*. Am J Surg 2006, 191:610-614 Beilman GJ, Blondet JJ, Nelson TR, Nathens AB, Moore FA, Rhee P, Puyana JC, Moore EE, Cohn SM. *Early hypothermia in severly injured trauma patients is a significant risk factor for multiple organ dysfunction syndrome but not mortality.* Ann Surg 2009, 249:845-850 Bukur M, Hadjibashi AA, Ley EJ, Malinoski D, Singer M, Barmparas G, Margulies D, Salim A. *Impact of prehospital hypothermia on transfusion requirements and outcomes*. J Trauma Acute Care Surg 2012, 73(5):1195-1201 Ireland S, Endacott R, Cameron P, Fitzgerald M, Paul E. *The incidence and significance of accidental hypothermia in major trauma – A prospective observational study*. Resuscitation 2011, 82:300-306 Martin RS, Kilgo PD, Miller PR, Hoth J, Meredith JW, Chang MC. *Injury-associated hypothermia: an analysis of the 2004 National Trauma Data Bank*. Schock 2005, 24(2):114-118 Seekamp A, Ziegler M, Van Griensven M, Grotz M, Regel G. *The role of hypothermia in trauma patients*. Eur J Emerg Med 1995, 2:28-32 Shafi S, Elliott AC, Gentilello L. *Is hypothermia simply marker of shock and injury severity or an independent risk factor for mortality in trauma patients? Analysis of a large National Trauma Registry.* J Trauma 2005, 56:1081-1085 Sundberg J, Estrada C, Jenkins C, Ray J, Abramo T. *Hypothermia is associated with poor outcome in pediatric trauma patients*. Am J Emerg Med 2011, 29:1019-1022 Thompson HJ, Kirkness CJ, Mitchell PH. *Hypothermia and rapid rewarming is associated with worse outcome following traumatic brain injury.* J Trauma Nurs 2010, 17(4):173-177 Waibel BH, Durham CA, Newell MA, Schlitzkus LL, Sagraves SG, Rotondo MF. *Impact of hypothermia in the rural, pediatric trauma patient.* Pediatr Crit Care Med 2010, 11(2):199-204 Wang HE, Callaway CW, Peitzman AB. *Admission hypothermia and outcome after major trauma*. Crit Care Med 2005, 33:1296-1301

Trauma – Active rewarming (First Aid)

Question (PICO)	Among people with severe bleeding/trauma (P) does a certain (re)warming technique (I) compared to another (re)warming technique (C) change the speed of rewarming and patient comfort (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the search terms: 1. [mh "Abdominal injuries"] or [mh "Multiple Trauma"] or [mh "Shock, Traumatic"] or [mh "Thoracic Injuries"] or [mh "Wounds, Nonpenetrating"] or [mh "Wounds, Penetrating"] or [mh Lacerations] or [mh "Vascular System Injuries"] or (trauma):ti,ab,kw or (traumatic NEXT injur*):ti,ab,kw or (bleeding):ti,ab,kw 2. hot:ti,ab,kw or warm:ti,ab,kw or Heat:ti,ab,kw or hot:ti,ab,kw or warm:ti,ab,kw or [mh "hypothermia"] or Hypothermia:ti,ab,kw or (body NEXT temperature):ti,ab,kw OR thermostasis:ti,ab,kw OR thermogenesis:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for guidelines, systematic reviews or experimental studies using the following search strategy: 1. "Hemorrhage"[Mesh] OR hemorrhage*[TIAB] OR bleeding[TIAB] OR Trauma[TIAB] OR traumatic injur*[TIAB] OR "lacerations"[Mesh] OR

	"wounds,nonpenetrating"[Mesh] OR laceration*[TIAB] OR "nonpenetrating wound"[TIAB] OR "nonpenetrating wounds"[TIAB] OR "nonpenetrating injury"[TIAB] OR "nonpenetrating injuries"[TIAB] OR "blunt injury"[TIAB] OR "blunt injuries"[TIAB] 2. Heat*[TIAB] OR hot[TIAB] OR warm*[TIAB] OR "Hot Temperature/therapeutic use"[Mesh] Or "Rewarming" [Mesh] OR "Hypothermia"[Mesh] OR Hypothermia[TIAB] OR "body temperature"[TIAB] OR thermostasis[TIAB] OR thermogenesis[TIAB] 3. "First Aid"[Mesh] OR "Community Health Workers"[Mesh] OR "Emergency Treatment"[Mesh:NoExp] OR "Emergency Medical Services"[Mesh:NoExp] OR "Emergency Service, Hospital"[Mesh] OR "Poison Control Centers"[Mesh] OR "Transportation of Patients"[Mesh] OR "Primary Health Care"[Mesh:NoExp] OR "Acute disease"[Mesh] OR "emergencies" [Mesh] OR "self care"[Mesh] OR "acute management" [TIAB] OR "immediate care" [TIAB] OR "prehospital treatment" [TIAB] OR "first aid"[TIAB] OR "self care"[TIAB] OR emergenc*[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) for systematic reviews or experimental studies using the following search strategy: 1. 'penetrating trauma'/exp OR 'laceration'/exp OR 'blunt trauma'/exp OR 'bleeding'/exp OR laceration*:ab,ti OR 'nonpenetrating wound':ab,ti OR 'nonpenetrating wounds':ab,ti OR 'nonpenetrating injury':ab,ti OR 'nonpenetrating injuries':ab,ti OR 'blunt injury':ab,ti OR 'blunt injuries':ab,ti OR hemorrhage*:ab,ti OR bleeding*:ab,ti OR 'bleeding'/exp OR Trauma:ab,ti OR (traumatic NEXT/1 injur*):ab,ti 2. Heat*:ab,ti OR hot:ab,ti OR warm*:ab,ti OR 'heat'/exp OR 'hypothermia'/exp OR hypothermia:ab,ti OR 'body temperature': ab,ti OR thermostasis:ab,ti OR thermogenesis:ab,ti 3. 'first aid'/exp OR 'health auxiliary'/exp OR 'emergency treatment'/de OR 'emergency health service'/exp OR 'poison center'/exp OR 'patient transport'/exp OR 'primary health care'/exp OR 'acute disease'/exp OR 'emergency'/exp OR 'self care'/exp OR 'acute management':ab,ti OR 'immediate care':ab,ti OR 'prehospital treatment':ab,ti OR 'self care':ab,ti OR 'first aid':ab,ti OR emergenc*:ab,ti 4. 1-3 AND Selected articles were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	12 March 2015
In/Exclusion criteria	**Population**: Include: trauma patients; Exclude: healthy volunteers **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available.

	An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies. **Language**: Include: English **Publication year**: Include: all years

Characteristics of included studies

Author, Year, Country	Study design	Population	Comparison	Remarks
Kober, 2001, Austria	Experimental: Randomised controlled trial	100 patients with minor trauma:50 were included in the passive rewarming group with core temperature 35.4°C; 50 were included in the active rewarming group with core temperature 35.3°C	passive warming (carbon-fiber electric non activated heating blanket + wool blanket) vs resistive heating (carbon-fiber electric activated heating blanket + wool blanket)	Duration of rescue transport (and rewarming): 64-69 minutes
Lundgren, 2011, Sweden	Experimental: Randomised controlled trial	51 trauma patients enrolled, 3 dropped out:22 were included in group 1 (passive rewarming); 26 in group 2 (active rewarming).	polyester blanket/ woolen blanket/ rescue blanket vs a chemical heat pad	Duration of rescue transport (and rewarming): 26±7 minutes

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Core temperature on arrival at hospital (°C) Mean±SD	passive warming vs resistive heating with electric heating blanket	Statistically significant: 35.0±0.2 vs 36.3±0.1 (p<0.001) *in favour of resistive heating* No effect size and CI reported. †	1, 50 vs 50§	Kober 2001
Rewarming rate (°C/h) Mean±SD		Statistically significant: -0.4±0.05 vs 0.8±0.08 (p<0.001) *in favour of resistive heating* No effect size and CI reported. †		
Number of patients (%) scoring overall patient care as good/very good		Statistically significant: 8% vs 96% (p<0.001) *in favour of resistive heating* No effect size and CI reported. †		
Core temperature on arrival at hospital (°C) Mean±SD	passive warming vs resistive heating with chemical pad	Not statistically significant: 36.0±0.3 vs 36.4±0.3 (p≥0.05) No effect size and CI reported. †	1, 22 vs 26§	Lundgren 2011
Cold discomfort (0= no sensation of cold; 10=unbearable sensation of cold) Median [IQR]		Not statistically significant: 3 [0-5] vs 2 [1-3] (p≥0.05) No effect size and CI reported. †		

† Imprecision (lack of data); § Imprecision (limited sample size)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Kober 2001	No	No	No	No	-Low number of participants.
Lundgren 2011	No	No	No	No	-Low number of participants.

Level of evidence

	High [A]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Small number of participants
Inconsistency	0	
Indirectness	-1	Use of a heating blanket/chemical pad (not available for laypersons)
Publication bias	0	
QUALITY (GRADE)	**Low [C]**	

Conclusion(s)	There is limited evidence neither in favour of active nor passive rewarming. In one study it was shown that resistive heating resulted in a statistically significant increase of rewarming rate, body temperature on arrival at hospital and patient comfort compared to passive heating (Kober 2001). In another study, a statistically significant increase of body temperature on arrival at hospital, using resistive heating compared passive warming could not be demonstrated. Evidence is of low quality and results of these studies are imprecise due to small number of participants.
Reference(s)	**Articles** Kober A, Scheck T, Fülesdi B, Lieba F, Vlach W, Friedman A, Sessler DI. *Effectiveness of resistive heating compared with passive warming in treating hypothermia associated with minor trauma: a randomized trial.* Mayo Clin Proc. 2001, 76(4):369-375. Lundgren P, Henriksson O, Naredi P, Björnstig U. *The effect of active warming in prehospital trauma care during road and air ambulance transportation - a clinical randomized trial.* Scand J Trauma Resusc Emerg Med. 2011, 19:59

RESUSCITATION

Resuscitation – Face shield (First Aid)

Question (PICO)	In humans who need to be resuscitated (P), is the use of a face shield (I) compared to not using a face shield (C) effective to successfully resuscitate a person (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: faceshield:ti,ab,kw OR "face shield":ti,ab,kw **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Resuscitation[Mesh] OR resuscitat*[TIAB] OR respirat*[TIAB] OR ventilat*[TIAB] 2. faceshield[TIAB] OR "face shield"[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Resuscitation/exp OR 'assisted ventilation'/exp OR ventilat*:ab,ti OR respirat*:ab,ti 2. faceshield:ab,ti OR 'face shield':ab,ti 3. 1-2 AND Guideline used as source for information: Perkins 2015 Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	13 November 2015
In/Exclusion criteria	**Population**: People who need to be resuscitated **Intervention**: Include: Face shield. Exclude: Pocket mask or bag-valve. **Comparison**: Include: mouth-to-mouth ventilation. Exclude: pocket mask or bag-valve. **Outcome**: Include: Tidal volume, minute volume, peak airway pressure, stomach inflation, ventilation quality. According to ERC (Perkins et al 2015) a tidal volume of 1L produces significantly more gastric inflation than a tidal volume of 500 ml. ERC (Perkins et al 2015) suggests a tidal volume of ±500-600 ml during adult CPR. Stomach inflation is associated with higher peak airway pressure (PAP). Exclude: prevention of oral bacterial flora transmission **Study design:** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Paal, 2006, Austria	Experimental: randomized controlled trial	70 unpaid, voluntary students (28 females, 42 males; mean age 17.3±0.7 years). Participants were separately instructed in the ILCOR 2000 guidelines. Teachers were experienced in CPR. The ventilation technique was explained and demonstrated by the instructor and finally performed by the candidate on a Laerdal Little Anne™.	1. Mouth-to-mouth ventilation (MMV): n=24 2. Mouth-to-pocket mask ventilation (MPV): n=25 3. Mouth-to-face shield ventilation (MFV): n=21 [Only data on MFV vs MMV were extracted]	According to ERC (Perkins et al 2015) a tidal volume of 1L produces significantly more gastric inflation than a tidal volume of 500 ml. ERC (Perkins et al 2015) suggests a tidal volume of ±500-600 ml during adult CPR. Stomach inflation is associated with higher PAP.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Ventilation quality meeting the recommended tidal volume of 700-1000 ml	MFV vs MMV	Not statistically significant: 4/21 vs 4/24 OR: 1.18, 95%CI [0.25; 5.43] (p=0.84)* ¥	1, 21 vs 24 §	Paal, 2006
Tidal volume (ml)		Statistically significant: 694±360 vs 1038±408 MD: -344.00, 95%CI [-568.39; -119.61] (p=0.003)* *In favour of MFV*		
Peak airway pressure (cm H_2O)		Statistically significant: 9.96±6.05 vs 14.89±6.11 MD: -4.93, 95%CI [-8.49; -1.37] (p=0.007)* *In favour of MFV*		
Stomach inflation		Statistically significant: 9/21 vs 19/24 OR: 0.20, 95%CI [0.05; 0.73] (p=0.02)* *In favour of MFV*		

Mean ± SD (unless otherwise indicated)

* Calculations done by the reviewer(s) using Review Manager software

¥ Imprecision (large variability of results)

§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Paal, 2006	Unclear, randomization by distributing the alphabetically arranged candidates alternatively to two teaching rooms. In each room, a ventilation technique	No, outcome was measured by Bio Tek Ventilator tester and measurements were not revealed to volunteer. Participants who had completed the test were not allowed	No, the outcome was measured by Bio Tek Ventilator tester and outcome reporting was complete	No	Young study population. Use of manikin does not reflect real situation where rescuers are more prone to

	was assigned using a randomization table balanced for sex.	to talk with those who had not.			higher stress levels.

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/large variability of the results
Inconsistency	0	
Indirectness	-1	Lung capacity of a manikin is an indirect measure for survival of casualties
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is limited evidence in favour of mouth-to-face shield ventilation. It was shown that mouth-to-face-shield ventilation resulted in a statistically significant decrease of tidal volume and peak airway pressure, compared to mouth-to-mouth ventilation, with a tidal volume that is more in the range of the recommended tidal volume (Paal 2006). Furthermore, it was shown that mouth-to-face-shield ventilation resulted in a statistically significant decrease of stomach inflation, compared to mouth-to-mouth ventilation (Paal 2006). A statistically significant difference of ventilation quality, using mouth-to-face-shield compared to mouth-to-mouth ventilation, could not be demonstrated (Paal 2006). Evidence is of low quality and results cannot be considered precise due to limited sample size and/or large variability of results.
References	**Articles** Paal P, Falk M, Sumann G, Demetz F, Beikircher W, Gruber E, Ellerton J, Brugger H. *Comparison of mouth-to-mouth, mouth-to-mask and mouth-to-face-shield ventilation by lay persons*. Resuscitation 2006, 70:117-123 **Guidelines** Perkins GD, Handley AJ, Koster RW, Castrén M, Smyth MA, Olasveengen T, Monsiers K, Raffay V, Gräsner J-T, Wensel V, Ristagno G, Soar J, on behalf of the Adult basic life support and automated external defibrillation section Collaborators. *European Resuscitation Council Guidelines for Resuscitation 2015 Section 2. Adult basic life support and automated external defibrillation*. Resuscitation 2015, 95:81-99.

Resuscitation – Pocket mask (First Aid)

Question (PICO)	Among persons with a cardiac arrest (P), does resuscitation using a pocket mask for breathing (I) compared to resuscitation with mouth-to-mouth breathing (C) change survival (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search term: "pocket mask":ti,ab,kw **MEDLINE** (via PubMed interface) for systematic reviews, experimental or observational studies using the following search strategy: 1. "pocket mask"[TIAB] OR "pocket masks"[TIAB] OR "rescue mask" [TIAB] OR "rescue mask"[TIAB] OR "resuscitation mask"[TIAB] OR "CPR mask"[TIAB] 2. "cardiopulmonary resuscitation"[Mesh] OR "cardiopulmonary resuscitation"[TIAB] OR "heart arrest"[Mesh] OR "heart arrest"[TIAB] OR "cardiac arrest"[TIAB] OR "respiratory arrest"[TIAB] OR "respiration, artificial"[Mesh] 3. 1-2 AND **Embase** (via Embase.com interface) for systematic reviews, experimental or observational studies using the following search strategy: 1. 'pocket mask':ab:ti OR 'pocket masks':ab:ti OR 'rescue mask':ab:ti OR 'rescue masks':ab:ti OR 'CPR mask':ab:ti OR 'CPR masks':ab:ti 1. 'resuscitation'/exp OR 'resuscitation':ab:ti OR 'heart arrest'/exp OR 'heart arrest':ab:ti OR 'respiratory arrest'/exp OR 'respiratory arrest':ab:ti OR 'artificial ventilation'/exp OR 'artificial ventilation':ab:ti 2. 1-2 AND Guideline used as source for information: Perkins 2015 Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	13 November 2015
In/Exclusion criteria	**Population**: People who need to be resuscitated **Intervention**: Include: Pocket mask. Exclude: face shield or bag-valve. **Comparison**: Include: mouth-to-mouth ventilation. Exclude: face shield or bag-valve. **Outcome**: Include: Tidal volume, minute volume, peak airway pressure, stomach inflation, ventilation quality. According to ERC (Perkins et al 2015) a tidal volume of 1L produces significantly more gastric inflation than a tidal volume of 500 ml. ERC (Perkins et al 2015) suggests a tidal volume of ±500-600 ml during adult CPR. Stomach inflation is associated with higher peak airway pressure (PAP). Exclude: prevention of oral bacterial flora transmission **Study design:** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Adelborg, 2011, Denmark	Experimental: randomized controlled trial (within subjects design)	60 surf life guards in active service (mean age: 25.4±5.9 years, 40 male, 20 female) who completed the annual mandatory CPR re-training before commencing active service. Participants were randomized into 6 groups each performing three sessions of single-rescuer CPR on a manikin. Each session was of 3 min duration and separated by 5 min of rest. CPR was performed on a manikin.	1. mouth-to-mouth ventilation (MMV) 2. mouth-to-pocket mask ventilation (MPV) 3. bag-valve-mask ventilation (BMV) [data on BMV were not extracted]	
Paal, 2006, Italy	Experimental: randomized controlled trial	Volunteers (unpaid, students, mean age 17.3±0.7 years) without previous first aid education: 25 volunteers who performed mouth-to-pocket-mask ventilation vs. 24 volunteers who performed mouth-to-mouth ventilation on a manikin.	Mouth-to-pocket-mask ventilation (MPV) vs. mouth-to-mouth ventilation (MMV)	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
No-flow time (s) (= interruptions in chest compressions)	MPV vs. MMV	Statistically significant: 10.7±3.0 vs 8.9±1.6 MD: 1.8 (p<0.001) £ *In favour of MMV*	1, 60 vs 60 § (within subjects design)	Adelborg, 2011
Effective ventilations (defined as a ventilation duration of 1 s)		Statistically significant: 79% vs 91% MD: -12% (p>0.001) £ *In favour of MMV*		
Inspiratory time (s)		Not statistically significant: 0.7±0.2 vs 0.7±0.2 MD: 0 (p>0.05) £†		
Tidal volume (ml)		Not statistically significant: 600±300 vs 600±200 MD: 0 (p>0.05) £†		
		Not statistically significant: 893±442 vs 1038±408 MD: -145, 95% CI [-383.04; 93.04] (p=0.23) *	1, 25 vs 24 §	Paal, 2006
Time to start compression (s)		Not statistically significant: 23.1±10.2 vs 21.1±8.7 MD: 2.0 (p>0.05) £†	1, 60 vs 60 § (within subjects design)	Adelborg, 2011
Peak airway pressure (cm H_2O)		Not statistically significant: 12.47±7.21 vs 14.89±6.11 MD: -2.39, 95% CI [-6.13; 1.35] (p=0.21) *	1, 25 vs 24 §	Paal, 2006
Number with stomach inflation		Statistically significant: 13/25 (52%) vs 19/24 (79.2%) RR: 0.66 (p<0.05) ££ *In favour of MPV*		

Mean ± SD (unless otherwise indicated)

* The effect size and p-value were calculated by the reviewer(s) using the Review Manager Software

£ No CI available

££ No SD, effect size or CI available
† Imprecision (lack of data)
§ Imprecision (limited sample size)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Adelborg, 2011	Unclear, participants were randomized into 6 groups, but not mentioned how.	Unclear, not mentioned	No	Yes, effect on survival was not investigated	Use of manikins.
Paal, 2006	Unclear, the randomisation was accomplished by distritbuting the alpahabetically arranged candidates alternatively to the two teaching rooms. In each room, a ventilation technique was assigned using a randomisation table balanced for sex.	No, the outcome was measured by the Bio Tek Ventilator tester and the measurements were not revealed to the volunteer. Participants who had completed the test were not allowed to talk with those who had not.	No, the outcome was measured by the Bio Tek Ventilator tester and outcome reporting was complete	No	Young study population. Use of manikin does not reflect real situation where rescuers are more prone to highter stress levels.

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/lack of data
Inconsistency	0	
Indirectness	-1	Lung capacity of a manikin is an indirect measure for survival of casualties
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [C]**	

Conclusion	There is conflicting evidence from 2 experimental studies. It was shown that mouth-to-pocket mask ventilation resulted in a statistically significant increase of no-flow time (interruptions in chest compressions) and a decrease of effective ventilations, compared to mouth-to-mouth ventilation (Adelborg 2011). However, it was shown that mouth-to-pocket mask ventilation resulted in a statistically significant decrease of stomach inflation compared to mouth-to-mouth ventilation (Paal 2006). A statistically significant difference in outcomes related to the quality of the ventilation using mouth-to-pocket-mask ventilation compared to mouth-to-mouth ventilation, could not be demonstrated (Paal 2006). Evidence is of low quality and results of this study are imprecise due to limited sample size.
Reference(s)	**Articles** Adelborg K, Dalgas C, Grove EL, Jørgensen, Al-Mashhadi RH, Løfgren B. *Mouth-to-mouth ventilation is superior to mouth-to-pocket mask and bag-valve-mask ventilation during lifeguard CPR: A randomized study*. Resuscitation 2011, 82:618-622. Paal P, Falk M, Sumann G, Demetz F, Beikircher W, Gruber E, Ellerton J, Brugger H. *Comparison of mouth-to-mouth, mouth-to-mask and mouth-to-face-shield ventilation by lay persons*. Resuscitation 2006, 70(1):117-23.

	Guidelines Perkins GD, Handley AJ, Koster RW, Castrén M, Smyth MA, Olasveengen T, Monsiers K, Raffay V, Gräsner J-T, Wensel V, Ristagno G, Soar J, on behalf of the Adult basic life support and automated external defibrillation section Collaborators. *European Resuscitation Council Guidelines for Resuscitation 2015 Section 2. Adult basic life support and automated external defibrillation*. Resuscitation 2015, 95:81-99.

Resuscitation – Face shield vs pocket mask (First Aid)

Question (PICO)	In humans who need to be resuscitated (P), is the use of a face shield (I) compared to using a pocket mask (C) effective to successfully resuscitate a person (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: faceshield:ti,ab,kw OR "face shield":ti,ab,kw **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Resuscitation[Mesh] OR resuscitat*[TIAB] OR respirat*[TIAB] OR ventilat*[TIAB] 2. faceshield[TIAB] OR "face shield"[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Resuscitation/exp OR 'assisted ventilation'/exp OR ventilat*:ab,ti OR respirat*:ab,ti 2. faceshield:ab,ti OR 'face shield':ab,ti 3. 1-2 AND Guideline used as source for information: Perkins 2015 Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	13 November 2015
In/Exclusion criteria	**Population**: People who need to be resuscitated **Intervention**: Include: Mouth-to-face shield ventilation (MFV). Exclude: mouth-to-mouth or bag-valve ventilation. **Comparison**: Include: Mouth-to-pocket mask ventilation (MPV). Exclude: mouth-to-mouth or bag-valve ventilation. **Outcome**: Include: No-flow time, effective ventilations, tidal volume, minute volume, peak airway pressure, stomach inflation, ventilation quality. According to ERC (Perkins et al 2015) a tidal volume of 1L produces significantly more gastric inflation than a tidal volume of 500 ml. Exclude: prevention of oral bacterial flora transmission. **Study design:** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies.

	Language: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Adelborg, 2014, Denmark	Experimental: randomized controlled trial (within subjects design)	30 unpaid surf lifeguards, mean age 25.1±4.8 years, 9 females, 21 males. After inclusion, participants were formally trained in using MFV and MPV for approximately 15-30 min in total. They were randomly assigned to perform 2x3 min of single rescuer CPR using MFV and MPV on a resuscitation manikin. Each 3 min session was separated by a short break of approximately 5 min.	mouth-to-face shield ventilation (MFV) vs mouth-to-pocket mask ventilation (MPV)	Based on a pilot study (n=8, SD=1.6 s) it was calculated that 14 participants would be required to detect a 1.5 s difference in no-flow time at a significance level of 0.05 and a power of 90%.
Paal, 2006, Austria	Experimental: randomized controlled trial	70 unpaid, voluntary students (28 females, 42 males; mean age 17.3±0.7 years). Participants were instructed alone in the ILCOR 2000 guidelines. Teachers were experienced in CPR. The ventilation technique was explained and demonstrated by the instructor and finally performed by the candidate on a Laerdal Little Anne™.	4. Mouth-to-mouth ventilation (MMV): n=24 5. Mouth-to-pocket mask ventilation (MPV): n=25 6. Mouth-to-face shield ventilation (MFV): n=21 [Only data on MFV vs MPV were extracted]	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
No-flow time (s)	MFV vs MPV	Statistically significant: 8.6±1.7 vs 6.9±1.2 MD: 1.7 (p<0.0001) £ *In favour of MPV*	1, 30 vs 30 (within subjects; power analysis)	Adelborg, 2014
Effective ventilations (=visible chest rise)		Statistically significant: 199/242 vs 239/240 RR: 0.83 (p=0.0002) ££ *In favour of MPV*		
Tidal volume (ml)		Statistically significant: 360±200 vs 450±200 MD: -90 (p=0.006) £ *In favour of MPV*		
		Not statistically significant: 694±360 vs 893±442 MD: -199, 95%CI [-430.79; 32.79] (p=0.09)*	1, 21 vs 25 §	Paal, 2006

Ventilation quality meeting the recommended tidal volume of 700-1000 ml		Not statistically significant: 4/21 vs 8/25 OR: 0.50, 95%CI [0.13; 1.98] (p=0.32)* ¥		
Peak airway pressure (cm H_2O)		Not statistically significant: 9.96±6.05 vs 12.47±7.21 MD: -2.51, 95%CI [-6.34; 1.32] (p=0.20)* ¥		
Stomach inflation		Not statistically significant: 9/21 vs 13/25 OR: 0.69, 95%CI [0.22; 2.22] (p=0.54)* ¥		

Mean ± SD (unless otherwise indicated)
* Calculations done by the reviewer(s) using Review Manager software
£ No CI available
££ No effect size and CI available
¥ Imprecision (large variability of results)
§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Adelborg, 2014	Unclear, order of treatment was randomized but not mentioned how	Yes, but not possible to blind intervention	No	No	Use of manikin study does not reflect real situation where rescuers are more prone to higher stress levels.
Paal, 2006	Unclear, randomization by distributing the alphabetically arranged candidates alternatively to two teaching rooms. In each room, a ventilation technique was assigned using a randomization table balanced for sex.	No, outcome was measured by Bio Tek Ventilator tester and measurements were not revealed to volunteer. Participants who had completed the test were not allowed to talk with those who had not.	No, the outcome was measured by Bio Tek Ventilator tester and outcome reporting was complete	No	Young study population. Use of manikin does not reflect real situation where rescuers are more prone to higher stress levels.

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/large variability of the results
Inconsistency	0	
Indirectness	-1	Lung capacity of a manikin is an indirect measure for survival of casualties
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is limited evidence in favour of mouth-to-pocket mask ventilation (MPV). In making this evidence conclusion we place higher value on the important outcomes no-flow time and effective ventilations. It was shown that MPV resulted in a statistically significant decrease of no-flow time and increase of effective ventilations and tidal volume when compared to MFV (Adelborg, 2014). A statistically significant difference in tidal volume, ventilation quality, peak airway pressure and stomach inflation could not be demonstrated (Paal, 2006). Evidence is of low quality and results are imprecise due to limited sample sizes and/or large variability of results.
Reference(s)	**Articles** Adelborg K, Bjørnshave K, Mortensen MB, Espeseth E, Wolff A, Løfgren B. *A randomised crossover comparison of mouth-to-face-shield ventilation and mouth-to-pocket-mask ventilation by surf lifeguards in a manikin*. Anaestesia 2014, 69:712-716 Paal P, Falk M, Sumann G, Demetz F, Beikircher W, Gruber E, Ellerton J, Brugger H. *Comparison of mouth-to-mouth, mouth-to-mask and mouth-to-face-shield ventilation by lay persons*. Resuscitation 2006, 70:117-123 **Guidelines** Perkins GD, Handley AJ, Koster RW, Castrén M, Smyth MA, Olasveengen T, Monsiers K, Raffay V, Gräsner J-T, Wensel V, Ristagno G, Soar J, on behalf of the Adult basic life support and automated external defibrillation section Collaborators. *European Resuscitation Council Guidelines for Resuscitation 2015 Section 2. Adult basic life support and automated external defibrillation*. Resuscitation 2015, 95:81-99.

BLEEDING

Bleeding – Direct compression (First Aid)

Question (PICO)	Among persons with severe bleeding (P), does direct/manual compression (I) compared to no compression (C) change survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews) using the following search strategy: 1. [mh meta-analysis] OR meta analys*:ti,ab,kw OR meta-analys*:ti,ab,kw OR 'cochrane':ti,ab,kw OR 'embase':ti,ab,kw OR 'pubmed':ti,ab,kw OR 'medline':ti,ab,kw OR 'reference list':ti,ab,kw OR 'reference lists':ti,ab,kw OR 'bibliography':ti,ab,kw OR 'bibliographies':ti,ab,kw OR 'hand-search':ti,ab,kw OR 'manual search':ti,ab,kw OR 'selection criteria':ti,ab,kw OR 'relevant journals':ti,ab,kw 2. [mh laceration] OR [mh wounds,nonpenetrating] OR [mh hemorrhage] OR laceration*:ti,ab,kw OR 'nonpenetrating wound':ti,ab,kw OR 'nonpenetrating wounds':ti,ab,kw OR 'nonpenetrating injury':ti,ab,kw OR 'nonpenetrating injuries':ti,ab,kw OR 'blunt injury':ti,ab,kw OR 'blunt injuries':ti,ab,kw OR hemorrhage*:ti,ab,kw OR bleeding*:ti,ab,kw 3. pressure:ti,ab,kw OR compression:ti,ab,kw 4. 1-3 AND **Embase** (via Embase.com interface) for systematic reviews using the following search strategy: 1. 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti 2. 'laceration'/exp OR 'blunt trauma'/exp OR 'bleeding'/exp OR laceration*:ab,ti OR 'nonpenetrating wound':ab,ti OR 'nonpenetrating wounds':ab,ti OR 'nonpenetrating injury':ab,ti OR 'nonpenetrationg injuries':ab,ti OR 'blunt injury':ab,ti OR 'blunt injuries':ab,ti OR hemorrhage*:ab,ti OR bleeding*:ab,ti 3. 'manual pressure':ab,ti OR 'manual compression':ab,ti OR 'direct pressure':ab,ti OR 'direct compression':ab,ti OR 'indirect compression':ab,ti OR 'indirect pressure':ab,ti OR 'pressure point':ab,ti OR 'pressure points':ab,ti 4. 1-3 AND **MEDLINE** (via PubMed interface) for systematic reviews using the following search strategy: 1. "Guideline "[Publication Type] OR "Practice Guidelines as Topic"[Mesh] OR "Practice Guideline "[Publication Type] OR practice guideline*[TIAB])) OR Meta-Analysis as Topic[Mesh] OR meta analy*[TIAB] OR metaanaly*[TIAB] OR Meta-Analysis[Publication Type] OR systematic review*[TIAB] OR systematic overview*[TIAB] OR Review Literature as Topic[Mesh] OR cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB])) OR reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB] OR selection criteria[TIAB] OR data extraction[TIAB] AND Review[PT] NOT Comment[PT] OR Letter[PT] OR Editorial[PT] OR animal[Mesh] NOT animal[Mesh] AND human[Mesh] 2. "lacerations"[Mesh] OR "wounds,nonpenetrating"[Mesh] OR "hemorrhage"[Mesh] OR laceration*[TIAB] OR "nonpenetrating wound"[TIAB] OR "nonpenetrating wounds"[TIAB] OR "nonpenetrating injury"[TIAB] OR "nonpenetrating injuries"[TIAB]

	OR "blunt injury"[TIAB] OR "blunt injuries"[TIAB] OR hemorrhage*[TIAB] OR bleeding[TIAB] 3. "pressure"[TIAB] OR "compression"[TIAB] 4. 1-3 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	29 January 2015
In/Exclusion criteria	**Population:** people with (severe) bleeding. Population with deep venous thrombosis/ venous thromboembolism were also included. **Intervention:** Include: direct/manual compression, Exclude: other interventions related to control of bleeding such as elevation, indirect pressure, use of dressings or tourniquet. **Comparison:** Include: studies that compare direct/manual compression with no intervention. Also studies that compare direct/manual compression with other interventions to control bleeding were included. Outcome: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Study design:** Include: a systematic review/meta-analysis when the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. Relevant treatment recommendations of the American Heart Association (2010) and the International Federation of Red Cross Societies (2011) were also included. Exclude: Systematic reviews that did not report data of the individual studies separately were not included. Individual experimental/observational studies, case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies were also excluded.

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Biancari, 2010, Italy	Systematic review (and meta-analyses)	Adult patients undergoing any type of angiography and endovascular procedure. All studies involved patients in whom vascular access was achieved through the common femoral artery.	Intervention: Use of vascular closing devices (VasoSeal, AngioSeal, Techstar, Prostar, Duett, Perclose, X-Press,EVS, StarClose) Control: manual compression methods (no details about modalities were provided)	Only prospective, randomized studies with allocation to use of a vascular closing device or control including only manual compression methods were included (n=31)
Das,2010, United Kingdom	Systematic review (and meta-analyses)	All studies involving the four main vascular closing devices and manual compression in interventional procedures by way of femoral arterial access were included. All coronary or cardiac catheterization studies were excluded. The procedures	Intervention: Use of VCD (Angioseal, StarClose, Perclose or Duett) Control: Standard manual compression (Other less widely used devices (e.g., VasoSeal, QuickSeal) or adjuncts to manual compression (FemoStop) were not specifically included unless they were featured in a secondary minor capacity	13 comparative studies (4 randomized controlled trials)

		included were lower-limb (iliac and infrainguinal) arterial intervention (angiography, angioplasty, or stenting), renal artery intervention, uterine artery embolization (UAE), and transhepatic chemoembolization or radioembolization.	in a study that was already included.	
Jones, 2002, Australia	Systematic review (and meta-analyses)	Adult patients after cardiac investigational procedures in which a femoral sheath approach was used	Intervention: Mechanical compression Control: Manual compression (for 8-15 minutes)	Only randomized controlled trials were included in the meta-analysis
Koreny, 2004, Austria	Systematic review (and meta-analyses)	Patients undergoing coronary angiography or percutaneous vascular interventions.	Intervention: Use of VCD (VasoSeal, AngioSeal, Techstar, Prostar, Duett, Perclose) Control: (exclusive) manual compression	Only randomized controlled trials were included in the meta-analysis

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Risk of groin hematoma	VCD versus manual compression	Not statistically significant: 73/1420 vs 85/1294 § RR: 0.81, 95%CI [0.60;1.10] (p=0.18)* ¥	14, 1420 vs 1294	Biancari, 2010
		Not statistically significant: 54/1582 vs 48/791 § OR: 0.90, 95%CI [0.56;1.44] (p=0.66) ¥	10, 1582 vs 791	Das, 2010
		Not statistically significant: 105/1538 vs 114/1417 § RR: 0.93, 95%CI [0.66;1.30] (p=0.68)* ¥	15, 1538 vs 1417	Koreny, 2004
	Mechanical versus manual compression	Not statistically significant: 0/310 vs 7/333 § RR: 0.13, 95%CI [0.02;1.05] (p=0.06)* ¥	2, 310 vs 333	Jones, 2002
Risk of groin bleeding	VCD versus manual compression	Not statistically significant: 40/1136 vs 38/1032 § RR: 1.75, 95%CI [0.55;5.51] (p=0.34)* ¥	9, 1136 vs 1032	Biancari, 2010
		Not statistically significant: 49/971 vs 43/870 § RR: 1.71, 95%CI [0.71;4.08] (p=0.23)* ¥	8, 971 vs 870	Koreny, 2004
	Mechanical versus manual compression	Not statistically significant: 17/389 vs 18/416 § RR: 1.00, 95%CI [0.52;1.91] (p=1.00)* ¥	2, 389 vs 416	Jones, 2002

Risk of femoral pseudo aneurysm	Vascular closing devices versus manual compression	Not statistically significant: 35/1467 vs 21/1231 § RR: 1.34, 95%CI [0.80;2.25] (p=0.26)* ¥	15, 1467 vs 1231	Biancari, 2010
		Not statistically significant: 6/1582 vs 4/791 § OR: 0.37, 95%CI [0.07;1.89] (p=0.23) ¥	10, 1582 vs 791	Das, 2010
Risk of lower limb ischemia and/or arterial stenosis		Not statistically significant: 2/1117 vs 0/1098 § RR: 5.03, 95%CI [0.24; 103.97] (p=0.30)* ¥	11, 1117 vs 1098	Biancari, 2010
		Not statistically significant: 12/1582 vs 5/791 § OR: 1.00, 95%CI [0.33;3.03] (p=0.59) ¥	10, 1582 vs 791	Das, 2010
Risk of groin infection		Statistically significant: 13/1463 vs 3/1445 § RR: 3.28, 95%CI [1.03;10.39] (p=0.04) * *In favour of manual compression*	13, 1463 vs 1445	Biancari, 2010
Risk of blood transfusion		Not statistically significant: 3/1273 vs 6/1303 § RR: 0.78, 95%CI [0.13;4.53] (p=0.78)* ¥	14, 1273 vs 1303	
Risk of arterial complications		Not statistically significant: 10/1856 vs 7/1600 § RR: 1.32, 95%CI [0.50;3.51] (p=0.58)* ¥	17, 1856 vs 1600	
Time to haemostasis (minutes)		Statistically significant: MD: -13.68, 95%CI [-14.45;-12.91] (p<0.00001) * *In favour of vascular closing devices*	9, 819 vs 702 §	
Need for vascular surgery		Not statistically significant: 14/1582 vs 6/791 § OR: 0.75, 95%CI [0.28;2.04] (p=0.52) ¥	10, 1582 vs 791	Das, 2010
Risk of total complication rate		Not statistically significant: 90/1582 vs 65/791 § OR: 0.87, 95%CI [0.52;1.48] (p=0.13) ¥		

*Calculations done by the reviewer(s) using Review Manager software
¥ Imprecision (large variability of results)
§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Information about 'limitations of study design' from the SR
Biancari,2010	No study quality assessment was performed
Das,2010	Non-randomised trials: scoring system = MINORS, Randomised trials: scoring system = Jadad score. No summarized information available in the text.
Jones,2002	Studies were excluded from meta-analysis if they had • an inadequately defined randomization technique (selection bias) • apart from the study intervention, had a difference in care within the study groups (performance bias) • had different treatment groups because participants withdrew or dropped out from the study (attrition bias) • had different outcome assessment measures (detection bias)

Koreny,2004	Six studies (20%) reported allocation concealment. Four studies (13%) explicitly reported an intention-to-treat analysis (in another 15 studies (50%) such an analysis was possible). Three studies (10%) explicidy reported blinded outcome assessment. There were only 2 studies (7%) in which allocation concealment, intention-to-treat analysis, and blinded outcome assessment were reported.

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'limitations in study design'
Imprecision	-1	Large variability of results and low number of events
Inconsistency	0	
Indirectness	-1	Intervention (absence of direct comparison between manual compression and no compression, only comparison with mechanical compression and/or vascular closing devices was studied. Population (intervention was performed by trained medical personnel in a hospital setting)
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Conclusion	No evidence could be identified comparing manual compression versus no manual compression in case of bleeding. There is limited evidence from 4 systematic reviews comparing vascular closing devices versus manual compression in case of bleeding (Biancari 2010, Das 2010, Jones 2002, Koreny 2004). In these studies, a statistically significant increased risk of groin hematoma, groin bleeding, femoral pseudo aneurysm, lower limb ischemia and/or arterial stenosis, blood transfusion, arterial complications, the need for vascular surgery, total complication rate, using manual compression compared to vascular closing devices/mechanical compression, could not be demonstrated. However, Biancari 2010 found that a decreased risk of groin infection and an increased time to haemostasis was present when comparing manual compression with vascular closure devices/mechanical compression. Evidence is of very low quality and results of these studies are imprecise due to limited sample size and/or large variability of results.
Reference(s)	**Articles** Biancari F, D'Andrea V, Di MC;Savino G, Tiozzo V, Catania A. *Meta-analysis of randomized trials on the efficacy of vascular closure devices after diagnostic angiography and angioplasty*. Am Heart J 2010, 159:518-531 Das R, Ahmed K, Athanasiou T, Morgan RA, Belli AM. *Arterial closure devices versus manual compression for femoral haemostasis in interventional radiological procedures: a systematic review and meta-analysis.* Cardiovasc Intervent Radiol 2010, 34:723-738 Jones T, McCutcheon H. *Effectiveness of mechanical compression devices in attaining hemostasis after femoral sheath removal*. Am J Crit Care 2002, 11:155-162 Koreny M, Riedmuller E, Nikfardjam M, Siostrzonek P, Mullner M. *Arterial puncture closing devices compared with standard manual compression after cardiac catheterization: systematic review and meta-analysis.* JAMA 2004, 291:350-357

Bleeding – indirect pressure (First aid)

Question (PICO)	Among persons with severe bleeding (P), does indirect pressure (I) compared to no indirect pressure (C) change survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews) using the following search strategy: 1. [mh meta-analysis] OR meta analys*:ti,ab,kw OR meta-analys*:ti,ab,kw OR 'cochrane':ti,ab,kw OR 'embase':ti,ab,kw OR 'pubmed':ti,ab,kw OR 'medline':ti,ab,kw OR 'reference list':ti,ab,kw OR 'reference lists':ti,ab,kw OR 'bibliography':ti,ab,kw OR 'bibliographies':ti,ab,kw OR 'hand-search':ti,ab,kw OR 'manual search':ti,ab,kw OR 'selection criteria':ti,ab,kw OR 'relevant journals':ti,ab,kw 2. [mh laceration] OR [mh wounds,nonpenetrating] OR [mh hemorrhage] OR laceration*:ti,ab,kw OR 'nonpenetrating wound':ti,ab,kw OR 'nonpenetrating wounds':ti,ab,kw OR 'nonpenetrating injury':ti,ab,kw OR 'nonpenetrating injuries':ti,ab,kw OR 'blunt injury':ti,ab,kw OR 'blunt injuries':ti,ab,kw OR hemorrhage*:ti,ab,kw OR bleeding*:ti,ab,kw 3. pressure:ti,ab,kw OR compression:ti,ab,kw 4. 1-3 AND **Embase** (via Embase.com interface) for systematic reviews using the following search strategy: 1. 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti 2. 'laceration'/exp OR 'blunt trauma'/exp OR 'bleeding'/exp OR laceration*:ab,ti OR 'nonpenetrating wound':ab,ti OR 'nonpenetrating wounds':ab,ti OR 'nonpenetrating injury':ab,ti OR 'nonpenetrationg injuries':ab,ti OR 'blunt injury':ab,ti OR 'blunt injuries':ab,ti OR hemorrhage*:ab,ti OR bleeding*:ab,ti 3. 'manual pressure':ab,ti OR 'manual compression':ab,ti OR 'direct pressure':ab,ti OR 'direct compression':ab,ti OR 'indirect compression':ab,ti OR 'indirect pressure':ab,ti OR 'pressure point':ab,ti OR 'pressure points':ab,ti 4. 1-3 AND **MEDLINE** (via PubMed interface) for systematic reviews using the following search strategy: 1. "Guideline "[Publication Type] OR "Practice Guidelines as Topic"[Mesh] OR "Practice Guideline "[Publication Type] OR practice guideline*[TIAB])) OR Meta-Analysis as Topic[Mesh] OR meta analy*[TIAB] OR metaanaly*[TIAB] OR Meta-Analysis[Publication Type] OR systematic review*[TIAB] OR systematic overview*[TIAB] OR Review Literature as Topic[Mesh] OR cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB])) OR reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB] OR selection criteria[TIAB] OR data extraction[TIAB] AND Review[PT] NOT Comment[PT] OR Letter[PT] OR Editorial[PT] OR animal[Mesh] NOT animal[Mesh] AND human[Mesh] 2. "lacerations"[Mesh] OR "wounds,nonpenetrating"[Mesh] OR "hemorrhage"[Mesh] OR laceration*[TIAB] OR "nonpenetrating wound"[TIAB] OR "nonpenetrating wounds"[TIAB] OR "nonpenetrating injury"[TIAB] OR "nonpenetrating injuries"[TIAB] OR "blunt injury"[TIAB] OR "blunt injuries"[TIAB] OR hemorrhage*[TIAB] OR bleeding[TIAB] 3. "pressure"[TIAB] OR "compression"[TIAB]

	4. 1-3 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	29 January 2015
In/Exclusion criteria	**Population:** people with (severe) bleeding. Population with deep venous thrombosis/ venous thromboembolism were also included. **Intervention:** Include: indirect pressure (applying pressure to the appropriate pressure point), Exclude: other interventions related to control of bleeding such as direct/manual compression, elevation, use of dressings or tourniquet. **Comparison:** Include: studies that compare indirect pressure with no intervention. Also studies that compare direct/manual compression with other interventions to control bleeding were included. Outcome: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Study design:** Include: a systematic review/meta-analysis when the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. Exclude: Systematic reviews that did not report data of the individual studies separately were not included. Individual experimental/observational studies, case series, cross-sectional studies, animal studies, *ex vivo* or *in vitro* studies were also excluded.

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Amputation – Keeping amputated body part on ice (First aid)

Question (PICO)	In humans with an amputated body part (P) does keeping the amputated body part on ice (I) compared to not keeping it on ice (C) change tissue healing, functional recovery, pain, complications, time to resumption of normal activities, restoration to the pre-exposure conditions (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "amutation, traumatic"] OR amputation:ti,ab,kw **MEDLINE** (via PubMed interface) for guidelines and systematic reviews using the following search strategy:

	1. "amputation, traumatic"[Mesh] OR amputation[TIAB] 2. Ice[Mesh] OR cryotherapy[Mesh:NoExp] OR Ice[TIAB] OR cryotherapy[TIAB] OR "cold therapy"[TIAB] OR preservation[TIAB] OR "Tissue preservation"[Mesh] OR conservation[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'traumatic amputation'/exp OR amputation:ab,ti 2. Ice/exp OR 'cryotherapy'/de OR ice:ab,ti OR cryotherapy:ab,ti OR 'cold therapy':ab,ti OR preservation:ab,ti OR 'tissue preservation'/exp OR conservation:ab,ti 3. 1-2 AND
Search date	2 April 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Bruise – Ice (First Aid)

Question (PICO)	In humans with a bruise (P), does ice (I) compared to no ice (C) increase tissue healing, functional recovery, pain, complications, time to resumption of usual activities, restoration to the pre-exposure condition and time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh contusions] OR contusion*:ti,ab,kw OR bruis*:ti,ab,kw 2. [mh ice] OR [mh cryotherapy] OR ice:ti,ab,kw OR cryotherapy:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. contusions[Mesh] OR bruise*[TIAB] OR contusion*[TIAB] 2. ice[Mesh] OR cryotherapy[Mesh] OR ice[TIAB] OR cryotherapy[TIAB] OR cold [TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'skin bruising'/exp AND 'contusion'/exp OR contusion*:ab,ti OR bruis*:ab,ti 2. 'ice'/exp OR 'cryotherapy'/de OR ice:ab,ti OR cryotherapy:ab,ti OR cold:ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	09 April 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Mayo, 2013, USA	Experimental: randomized controlled trial (within subjects design)	17 healthy patients (4 male, 13 female), mean age 28 years. Bruises were induced using a 595-nm wavelength PDL. Single pulses were administered in a non-overlapping fashion achieving a 2- by 2-cm bruise within 1 minute. Five similar zones of bruising were induced on the lower abdomen in a band-like distribution.	1. Bruise serum 2. 3% OTC hydrogen peroxide-soaked gauze 3. Cold compress 4. PDL 5. Control: no treatment Treatments were 10 minutes long and were initiated immediately after bruise induction. [Data on bruise serum, hydrogen peroxide and PDL will not be extracted]	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Bruise severity (VAS)	Cold compress vs control	Day 0: Not statistically significant: 4.8±3.0 vs 6.4±2.8 MD: -1.6 (p=0.11) Day 3: Not statistically significant: 3.5±2.7 vs 4.2±2.8 MD: -0.7 (p=0.47) Day 7: Not statistically significant: 1.0±1.2 vs 1.3±1.4 MD: -0.3 (p=0.53)	1, 17 vs 17 § (within subjects)	Mayo, 2013

Mean ± SD (unless otherwise indicated)
§ Imprecision (limited sample size)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Mayo, 2013	Yes, not mentioned if and how allocation was done	Yes, participants were not blinded	No	No	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is limited evidence from 1 experimental study, neither in favour of the intervention nor the control. A statistically significant decrease of bruise severity, using a cold compress compared to no treatment, could not be demonstrated (Mayo 2013). Evidence is of low quality and results of this study are imprecise due to limited sample size, lack of data and/or large variability of results.
Reference(s)	**Articles** Mayo TT, Khan F, Hunt C, Fleming K, Markus R. *Comparative study on bruise reduction treatments after bruise induction using the pulsed dye laser*. Dermatol Surg 2013, 39:1459-1464

Crush injury – Extraction (First Aid)

Question (PICO)	In humans who are crushed by a heavy object (P) does extracting this person (I) compared to not extracting (C) increase survival, tissue healing, functional recovery, pain, complications, time to resumption of usual activities, restoration to pre-exposure condition and time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "crush syndrome"] OR "crush injur*":ti,ab,kw OR "crush trauma":ti,ab,kw OR "crush syndrome":ti,ab,kw **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Crush syndrome"[Mesh] OR "crush injur*"[TIAB] OR "crush injuries"[TIAB] OR "crush trauma"[TIAB] OR "crush syndrome"[TIAB] 2. Extract*[TIAB] OR extricat*[TIAB] OR "Rescue work"[Mesh] OR rescu*[TIAB] OR "first aid"[Mesh] OR "first aid"[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'crush trauma'/exp OR 'crush injury':ab,ti OR 'crush injuries':ab,ti OR 'crush syndrome':ab,ti OR 'crush trauma':ab,ti OR 'crush traumas':ab,ti 2. 'extraction'/exp OR extract*:ab,ti OR extricat*:ab,ti OR 'rescue work'/exp OR rescu*:ab,ti OR 'first aid'/exp OR 'first aid':ab,ti 3. 1-2 AND
Search date	16 April 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. Studies concerning the medicinal treatment of crush injuries by EMS personnel. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers.

	Design: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Crush injury – Extraction (timing) (First Aid)

Question (PICO)	In humans who are crushed by a heavy object (P) does extracting the victim after 15 minutes, 30 minutes or 2 hours (I) compared to immediately extracting the victim (C) increase survival, tissue healing, functional recovery, pain, complications, time to resumption of usual activities, restoration to pre-exposure condition and time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "crush syndrome"] OR "crush injur*":ti,ab,kw OR "crush trauma":ti,ab,kw OR "crush syndrome":ti,ab,kw **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Crush syndrome"[Mesh] OR "crush injur*"[TIAB] OR "crush injuries"[TIAB] OR "crush trauma"[TIAB] OR "crush syndrome"[TIAB] 2. Extract*[TIAB] OR extricat*[TIAB] OR "Rescue work"[Mesh] OR rescu*[TIAB] OR "first aid"[Mesh] OR "first aid"[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'crush trauma'/exp OR 'crush injury':ab,ti OR 'crush injuries':ab,ti OR 'crush syndrome':ab,ti OR 'crush trauma':ab,ti OR 'crush traumas':ab,ti 2. 'extraction'/exp OR extract*:ab,ti OR extricat*:ab,ti OR 'rescue work'/exp OR rescu*:ab,ti OR 'first aid'/exp OR 'first aid':ab,ti 3. 1-2 AND
Search date	16 April 2015

In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. Studies concerning the medicinal treatment of crush injuries by EMS personnel. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Nasal bleeding – Posture (First Aid)

Question (PICO)	In humans with a nosebleed (P), does a certain posture (I) compared to another posture (C) increase tissue healing, functional recovery, pain, complications, time to resumption of usual activities, restoration to the pre-exposure condition and time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh epistaxis] or epistaxis:ti,ab,kw or nosebleed*:ti,ab,kw or "nose bleed*":ti,ab,kw or "nasal bleed*":ti,ab,kw 2. [mh ice] or [mh cryotherapy] or ice*:ti,ab,kw or cryotherapy:ti,ab,kw OR [mh "Posture"] OR Posture:ti,ab,kw OR Position:ti,ab,kw

	3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Epistaxis[Mesh] OR nosebleed*[TIAB] OR epistaxis[TIAB] OR "nose bleed*"[TIAB] OR "nasal bleed*"[TIAB] 2. Ice[Mesh] OR ice*[TIAB] OR cryotherapy[Mesh] OR cryotherapy[TIAB] OR Posture[Mesh] OR position*[TIAB] OR posture[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Epistaxis/exp OR epistaxis:ab,ti OR nosebleed*:ab,ti OR (nose NEXT/1 bleed*):ab,ti OR (nasal NEXT/1 bleed*):ab,ti 2. Ice/exp OR ice*:ab,ti OR cryotherapy/exp OR cryotherapy:ab,ti OR 'body position'/exp OR position*:ab:ti OR 'posture':ab:ti 3. 1-2 AND
Search date	10 April 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Nasal bleeding – Ice collar (First Aid)

Question (PICO)	In humans with a nosebleed (P), does an ice collar (I) compared to no ice collar (C) increase tissue healing, functional recovery, pain, complications, time to resumption of usual activities, restoration to the pre-exposure condition and time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh epistaxis] or epistaxis:ti,ab,kw or nosebleed*:ti,ab,kw or "nose bleed*":ti,ab,kw or "nasal bleed*":ti,ab,kw 2. [mh ice] or [mh cryotherapy] or ice*:ti,ab,kw or cryotherapy:ti,ab,kw OR [mh "Posture"] OR Posture:ti,ab,kw OR Position:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Epistaxis[Mesh] OR nosebleed*[TIAB] OR epistaxis[TIAB] OR "nose bleed*"[TIAB] OR "nasal bleed*"[TIAB] 2. Ice[Mesh] OR ice*[TIAB] OR cryotherapy[Mesh] OR cryotherapy[TIAB] OR Posture[Mesh] OR position*[TIAB] OR posture[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Epistaxis/exp OR epistaxis:ab,ti OR nosebleed*:ab,ti OR (nose NEXT/1 bleed*):ab,ti OR (nasal NEXT/1 bleed*):ab,ti 2. Ice/exp OR ice*:ab,ti OR cryotherapy/exp OR cryotherapy:ab,ti OR 'body position'/exp OR position*:ab:ti OR 'posture':ab:ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	10 April 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available.

	An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Teymoortash, 2003, Germany	Experimental: Randomized controlled trial (within subjects design)	56 healthy volunteers (29 women, 27 men), mean age 30 years. Nasal mucosal microcirculatory blood flow was measured with and without application of ice collar.	Ice collar vs no ice collar	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Nasal mucosal blood flow	Ice collar vs no ice collar	Not statistically significant: 1130.5±792.2 vs 1368.8±927.9 MD: -238.3 (p=0.11)	1, 56 vs 56 § (within subjects)	Teymoortash, 2003
Total nasal inspiratory airflow		Not statistically significant: 471.5±164.6 vs 513.9±190.4 MD: -42.4 (p=0.08)		
Total nasal expiratory airflow		Not statistically significant: 443.1±162.4 vs 474.2±211.7 MD: -31.1 (p=0.30)		

Mean ± SD (unless otherwise indicated)

¥ Imprecision (large variability of results)

§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Teymoortash, 2003	Yes, but not possible	Yes, but not possible	No	No	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/large variability of the results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is limited evidence from 1 experimental study, neither in favour of the intervention nor the control. A statistically significant decrease of nasal mucosal bloodflow and nasal airflow, using ice collar compared to no ice collar, could not be demonstrated (Teymoortash 2003). Evidence is of low quality and results of this study are imprecise due to limited sample size, lack of data and/or large variability of results.
Reference(s)	**Articles** Teymoortash A, Sesterhenn A, Kress R, Sapundzhiev N. *Efficacy of ice packs in the management of epistaxis*. Clin Otolaryngol 2003, 28:545-547

Nasal bleedings – Humidity (Prevention)

Question (PICO)	In humans (P), is a good air humidity (I), compared to dry air (C) effective to prevent nosebleeds (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh epistaxis] or epistaxis:ti,ab,kw or nosebleed*:ti,ab,kw or "nose bleed*":ti,ab,kw or "nasal bleed*":ti,ab,kw 2. [mh prevention] OR "prevention":ti,ab,kw OR [mh humidity] OR humidity:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Epistaxis[Mesh] OR nosebleed*[TIAB] OR epistaxis[TIAB] OR "nose bleed*"[TIAB] OR "nasal bleed*"[TIAB] 2. "Accident Prevention"[Mesh] OR "Primary Prevention"[Mesh:NoExp] OR "Health Education"[Mesh] OR "Health Behavior"[Mesh] OR "prevention and control"[Subheading] OR "Health promotion"[Mesh] OR humidity[Mesh] OR humidity[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Epistaxis/exp OR epistaxis:ab,ti OR nosebleed*:ab,ti OR (nose NEXT/1 bleed*):ab,ti OR (nasal NEXT/1 bleed*):ab,ti 2. 'prevention'/exp OR prevention:ti,ab OR humidity/exp OR humidity:ab,ti 3. 1-2 AND
Search date	07 May 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included (but considered as indirect evidence). In case of preventive interventions: studies on primary prevention of injuries and diseases at household or community levels that describe interventions with a potential immediate effect. Studies on preventive programmes or campaigns that consist of training or provision of an information leaflet, booklet, sticker. Exclude: Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. Secondary or tertiary prevention. Interventions at policy level. Interventions based on drugs or vaccines. The following programmes: one-to-one programmes, home safety checks, free provision of materials, peer tutoring, information from medical doctors. Studies specifically intended for industrially specific situations (workplace related)

	Outcome: Include: health outcome measures (including adverse effects). Studies on the incidence of accidents. Exclude: studies on feasibility of or compliance with interventions (behavioural outcomes). Measures of knowledge or attitudes. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies. Studies in which results are only discussed in a narrative way, without raw data. **Language**: Include: English **Publication year:** Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Nasal bleedings – Nose picking (Risk Factor)

Question (PICO)	In humans (P), is nose picking (I) a risk factor for nosebleeds (O) compared to not nose picking (C)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh epistaxis] or epistaxis:ti,ab,kw or nosebleed*:ti,ab,kw or "nose bleed*":ti,ab,kw or "nasal bleed*":ti,ab,kw 2. [mh "risk factors"] OR "risk factor":ti,ab,kw OR "risk factors":ti,ab,kw OR "nose picking":ti,ab,kw OR [mh "environment, controlled"] OR "dry air":ti,ab,kw OR [mh sneezing] OR [mh altitude] OR altitude:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Epistaxis[Mesh] OR nosebleed*[TIAB] OR epistaxis[TIAB] OR "nose bleed*"[TIAB] OR "nasal bleed*"[TIAB] 2. "risk factors"[Mesh] OR "risk factor"[TIAB] OR "risk factors"[TIAB] OR "nose picking"[TIAB] OR "environment, controlled"[Mesh] OR sneezing[Mesh] OR altitude[Mesh] OR sneez*[TIAB] OR "dry air"[TIAB] OR altitude[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Epistaxis/exp OR epistaxis:ab,ti OR nosebleed*:ab,ti OR (nose NEXT/1 bleed*):ab,ti OR (nasal NEXT/1 bleed*):ab,ti

	2. 'risk factor'/exp OR 'risk factor':ab,ti OR 'risk factors':ab,ti OR 'nose picking':ab,ti OR 'microclimate'/exp OR 'dry air':ab,ti OR 'sneezing'/exp OR sneez*:ab,ti OR 'altitude'/exp OR altitude:ab,ti 3. 1-2 AND
Search date	07 May 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages at household level. Exclude: studies specifically intended for industrially specific situations (workplace related) **Risk factor**: Include: modifiable, proximal risk factor with a potential immediate implication for practice that results in primary prevention at the household or community level. Risk factors related to healthy persons. Exclude: risk factors that lead to interventions with already proven effectiveness. The risk factor that does not precede the outcome. The risk factor is common sense. **Outcome**: Include: health outcome measures **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies. **Language**: Include: English **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Nasal bleedings – Aspirin (Risk Factor)

Question (PICO)	In humans (P), is taking aspirin (I) a risk factor for nosebleeds (O) compared to not taking aspirin (C)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh epistaxis] or epistaxis:ti,ab,kw or nosebleed*:ti,ab,kw or "nose bleed*":ti,ab,kw or "nasal bleed*":ti,ab,kw 2. [mh "risk factors"] OR "risk factor":ti,ab,kw OR "risk factors":ti,ab,kw OR "nose picking":ti,ab,kw OR [mh "environment, controlled"] OR "dry air":ti,ab,kw OR [mh sneezing] OR [mh altitude] OR altitude:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Epistaxis[Mesh] OR nosebleed*[TIAB] OR epistaxis[TIAB] OR "nose bleed*"[TIAB] OR "nasal bleed*"[TIAB] 2. "risk factors"[Mesh] OR "risk factor"[TIAB] OR "risk factors"[TIAB] OR "nose picking"[TIAB] OR "environment, controlled"[Mesh] OR sneezing[Mesh] OR altitude[Mesh] OR sneez*[TIAB] OR "dry air"[TIAB] OR altitude[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Epistaxis/exp OR epistaxis:ab,ti OR nosebleed*:ab,ti OR (nose NEXT/1 bleed*):ab,ti OR (nasal NEXT/1 bleed*):ab,ti 2. 'risk factor'/exp OR 'risk factor':ab,ti OR 'risk factors':ab,ti OR 'nose picking':ab,ti OR 'microclimate'/exp OR 'dry air':ab,ti OR 'sneezing'/exp OR sneez*:ab,ti OR 'altitude'/exp OR altitude:ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	07 May 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages at household level. Exclude: studies specifically intended for industrially specific situations (workplace related) **Risk factor**: Include: modifiable, proximal risk factor with a potential immediate implication for practice that results in primary prevention at the household or community level. Risk factors related to healthy persons. Use of medication such as antiplatelet drugs. Exclude: risk factors that lead to interventions with already proven effectiveness. The risk factor that does not precede the outcome. The risk factor is common sense. **Outcome**: Include: health outcome measures **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies. **Language**: Include: English **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Risk factor	Remarks
Lubianca-Neto, 1998, Brazil	Observational: cross-sectional study	121 patients with hypertension, mean age 53.1±11.4 years (35 male, 86 female) randomly selected in a cross-sectional fashion	Aspirin use vs no aspirin use	The study was set up to evaluate the effect of a previous history of epistaxis and the severity of hypertension. Data on the occurrence of epistaxis and the use of aspirin were also obtained.
Rainsbury, 2009, UK	Observational: cohort study	10 241 patients with one or more episodes of epistaxis registered at three GP practices in Dudley, West Midlands between June 2003 and June 2008. Patients were divided in three groups based on repeat prescriptions of Aspirin (n=2492), Clopidogrel (n=365) or neither drug (n=7384)	Low-dose aspirin: 75 mg Clopidogrel: 75 mg No drug [data on Clopidogrel are not extracted]	
Soyka, 2010, Switzerland	Observational: cohort study	591 patients, median age 69.6 years (range 11.6-96.9 years), 331 males, 260 females; suffering from epistaxis in the period from March 29, 2007 to April 1, 2008. Patients were divided in intake of acetylsalicylic acid (n=198) or no intake of acetylsalicylic acid (n=393)	Intake of acetylsalicylic acid (ASA) vs no intake of acetylsalicylic acid (no ASA).	

Synthesis of findings

Outcome	Risk factor	Effect Size	#studies, # participants	Reference
Epistaxis	Asprin vs no aspirin	Statistically significant: 13/36 vs 15/84 § RR: 2.02, 95%CI [1.08; 3.80] (p=0.03) *With harm for aspirin*	1, 36 vs 84	Lubianca-Neto, 1998
	Aspirin vs no drug	Statistically significant: 48/2492 vs 16/7384 § OR: 9.05, 95%CI [5.13; 15.96], (p<0.0001) *With harm for aspirin*	1, 2492 vs 7384	Rainsbury, 2009
Recurrent epistaxis	ASA vs no ASA	Statistically significant: 38/198 vs 50/393 § OR: 1.63, 95%CI [1.03; 2.59] (p=0.04)* *With harm for acetylsalicylic acid*	1, 198 vs 393	Soyka, 2010

* Calculations done by the reviewer(s) using Review Manager software

§ Imprecision (low number of events)

Quality of evidence

Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations
Lubianca-Neto, 1998	No, patients were randomly selected	No	No, they controlled for confounding factors	No	
Rainsbury, 2009	No, groups were matched for age and sex	No	Yes, controlled for hypertension as confounding factor, but not for other factors such as rhinitis, nasal trauma or surgery, other NSAIDs, alcohol and weather	No	
Soyka, 2010	Unclear	No	Yes, confounding factors were mentioned but not included in the analysis	No	

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Low number of events
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Conclusion	There is limited evidence from 3 observational studies with harm for acetylsalicylic acid (aspirin). It was shown that taking aspirin resulted in a statistically significant increased risk of epistaxis (nosebleeds), compared to not taking aspirin (Lubianca-Neto 1998, Rainsbury 2009, Soyka 2010). Evidence is of very low quality and results cannot be considered precise due to low number of events.
Reference(s)	**Articles** Lubianca-Neto JF, Bredemeier M, Carvalhal EF, Arruda CA, Estrella E, Pletsch A, Gus M, Lu L, Fuchs FD. *A study of the Association Between Epistaxis and the Severity of Hypertension*. Am J Rhinology 1998, 12:269-272 Rainsbury JW and Molony NC. *Clopidogrel versus low-dose aspirin as risk factor for epistaxis*. Clin Otolaryngol 2009, 34:232-235 Soyka MB, Rufibach K, Huber A, Holzmann D. *Is severe epistaxis associated with acetylsalicylic acid intake?* Laryngoscope 2010, 120:200-207

Bleeding from ear – Position (First Aid)

Question (PICO)	In humans who are bleeding from the ear (P), does a certain posture (I) compared to another posture (C) increase tissue healing, functional recovery, pain, complications, time to resumption of usual activities, restoration to the pre-exposure condition and time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. (Bleed*:ti,ab,kw OR blood*:ti,ab,kw OR discharge:ti,ab,kw) AND (ear:ti,ab,kw OR [mh ear]) 2. [mh posture] OR posture:ti,ab,kw OR position:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. (bleed*[TIAB] OR blood*[TIAB] OR discharge[TIAB]) AND (ear[TIAB] OR ear[Mesh]) 2. Posture[Mesh] OR posture[TIAB] OR position[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'ear injury'/exp OR ((Bleed*:ab,ti OR blood*:ab,ti OR discharge:ab,ti) AND (ear:ab,ti OR ear/exp)) 2. 'head position'/exp OR posture:ab,ti OR position:ab,ti 3. 1-2 AND
Search date	17 April 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

SKIN WOUNDS

Cuts and grazes – Irrigating with water (First Aid)

Question (PICO)	In humans with cuts and grazes (P), is irrigating the wound with water (I) compared to other treatments (C) effective to change tissue healing, functional recovery, pain, complications, time to resumption of usual activities, restoration to the pre-exposure condition, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Wound, penetrating"] OR [mh lacerations] OR Wound:ti,ab,kw OR wounds:ti,ab,kw OR laceration:ti,ab,kw OR lacerations:ti,ab,kw OR cut:ti,ab,kw OR cuts:ti,ab,kw OR graze:ti,ab,kw OR grazes:ti,ab,kw 2. water:ti,ab,kw AND (cleans*:ti,ab,kw OR irrigat*:ti,ab,kw) 3. 1-2 AND **MEDLINE** (via PubMed interface) using the following search strategy: 1. wounds, penetrating[Mesh] OR lacerations[Mesh] OR wound[TIAB] OR wounds[TIAB] OR laceration[TIAB] OR lacerations[TIAB] OR cut[TIAB] OR cuts[TIAB] OR graze[TIAB] OR grazes[TIAB] 2. water[TIAB] AND (cleans*[TIAB] OR irrigat*[TIAB]) 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'penetrating trauma'/exp OR 'laceration'/exp OR 'wound'/exp OR wound:ab,ti OR wounds:ab,ti OR laceration:ab,ti OR lacerations:ab,ti OR cut:ab,ti OR cuts:ab,ti OR graze:ab,ti OR grazes:ab,ti 2. Water:ab,ti AND (cleans*:ab,ti OR irrigat*:ab,ti) 3. 1-2 AND Guidelines, systematic reviews, retrieved with the above searches, and used as source for individual studies: Fernandez, 2012
Search date	18 February 2015
In/Exclusion criteria	**Population:** Include: sick or injured people or healthy volunteers of all ages. Trials involving people of all ages with a wound. A wound is defined as a break in the skin. **Intervention:** Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). The solutions should be used specifically for wound cleansing. Wound cleansing is defined as: "the use of fluids to remove loosely adherent debris and necrotic tissue from the wound surface". We included trials evaluating the use of water compared with no cleaning or with another treatment. Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. We excluded trials that used pre-operative skin cleansing to prevent postoperative infections, trials that assessed the effectiveness of solutions as part of the operative procedure, trials that used a solution as a prophylactic treatment, and trials involving post-operative wound care.

	Outcome: Include: wound infection, proportion of wounds that healed, rate of wound healing, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomized controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Angeras, 1992, Sweden	Experimental: quasi-randomized controlled trial	705 patients with soft tissue wounds less than 6 hours old, requiring sutures. Wounds were irrigated with tap water (n=295) or saline (n=322)	1) Wounds irrigated with tap water at 37°C 2) Wounds irrigated with sterile normal saline at room temperature	
Bansal, 2002, USA	Experimental: randomized controlled trial	46 children with simple lacerations that were cleansed with tap water (n=21) or saline (n=24)	1) Cleansing with tap water 2) Cleansing with saline Wound was irrigated with 35 ml syringe attached to an irrigation shield	
Godinez, 2002, USA	Experimental: randomized controlled trial	94 participants with minor extremity lacerations had their wounds irrigated with tap water (n=36) or saline (n=41)	1) Cleansing with tap water: wounds were irrigated at a flow of 7 litres/minute 2) Cleansing with saline: saline was poured in a basin and aspirated using a syringe and irrigation was done using a pulsatile motion	
Griffiths, 2001, Australia	Experimental: randomized controlled trial	35 patients with chronic wounds which were irrigated with tap water (n=23) or normal saline (n=26)	1) Irrigation with tap water 2) Irrigation with normal saline	
Moscati, 2007, USA	Experimental: randomized controlled trial	715 subjects with uncomplicated skin lacerations requiring staple or suture repair. Wounds were irrigated with tap water (n=300) or sterile saline (n=334)	1) Irrigation with tap water 2) Irrigation with minimum 200 ml of sterile saline Irrigation with tap water was undertaken by patient, while irrigation with sterile saline was undertaken by the provider.	

			Wounds were irrigated with a 35 ml syringe using a splash guard.	
Valente, 2003, USA	Experimental: quasi-randomized controlled trial	530 children with simple lacerations. Wounds were cleansed with tap water (n=259) or saline (n=271)	1) Cleansing with tap water: wounds were irrigated under running tap water for 10 seconds. 2) Cleansing with saline: wounds were irrigated using a 30-60 ml syringe and a 18G angiocatheter or splash guard.	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Infection (acute wounds)	Tap water vs normal saline	Not statistically significant: 28/631 vs 47/697§ RR: 0.66, 95%CI [0.42, 1.04] (p=0.071)¥	3, 631 vs 697 (Angeras 1992, Godinez 2002, Moscati 2007, cited in Fernandez 2012)	Fernandez, 2012
		Not statistically significant: 9/260 vs 9/275§ RR: 1.07, 95%CI [0.43, 2.64] (p=0.88)¥	2, 260 vs 275 (Bansal 2002, Valente 2003, cited in Fernandez 2012)	Fernandez, 2012
Infection (chronic wounds)		Not statistically significant: 0/23 vs 3/26§ RR: 0.16, 95%CI [0.01, 2.96] (p=0.22)¥	1, 23 vs 26 § (Griffiths, cited in Fernandez 2012)	Fernandez 2012
Healing		Not statistically significant: 8/23 vs 16/26 RR: 0.57, 95%CI [0.30, 1.07] (p=0.08)¥		

¥ Imprecision (large variability of results)

§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Angeras, 1992	Yes, allocation by alternation	Unclear, not stated	No	No	
Bansal, 2002	No, allocation using randomization schedule	No, person performing wound irrigation was blinded to solution used	No	No	
Godinez, 2002	Unclear, not stated	Unclear, not stated	No	No	
Griffiths, 2001	No, allocation by a closed list of random numbers	No, patient and outcome assessors were blinded to treatment	No	No	
Moscati, 2007	No, allocation using computer based random numbers generator	No, outcome assessor was blinded to solution used	No	No	
Valente, 2003	Yes, allocation by alternation	Unclear, not stated	No	No	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Low number of events/large variability of the results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Moderate [B]**	

Conclusion	There is limited evidence, neither in favour of the intervention nor the control: A statistically significant decrease of infection, using tap water compared to saline, could not be demonstrated (Angeras 1992, Bansal 2002, Godinez 2002, Griffiths 2001, Moscati 2007, Valente 2003). A statistically significant increase of healing, using tap water compared to saline, could not be demonstrated (Griffiths 2001). Evidence is of moderate quality and results of these studies are imprecise due to limited event size and large variability of results.
Reference(s)	**Articles** Angeras MH, Brandberg A, Falk A, Seeman T. *Comparison between sterile saline and tap water for the cleaning of acute traumatic soft tissue wounds*. European Journal of Surgery 1992, 158(6-7):347-50 Bansal BC, Wiebe RA, Perkins SD, Abramo TJ. *Tap water for irrigation of lacerations*. Am J Emerg Med 2002, 20(5):469-72 Godinez FS, Grant-Levy TR, McGuirk TD, Letterle S, Eich M, O'Malley GF. *Comparison of normal saline vs tap water for irrigation of minor lacerations in the emergency department*. Academic Emergency Medicine 2002, 19(5):396-7 Griffiths RD, Fernandez RS, Ussia CA. *Is tap water a safe alternative to normal saline for wound irrigation in the community setting*. Journal of Wound Care 2001, 10(10):407-11 Moscati RM, Mayrose J, Reardon RF, Janicke DM, Jehle DV. *A multicentre comparison of tap water versus sterile saline for wound irrigation.* Academic Emergency Medicine 2007, 14:404-10 Valente JH, Forti RJ, Freundlich LF, Zandieh SO, Crain EF. *Wound irrigation in children: saline solution or tap water?* Annals of Emergency Medicine 2003, 41:609-16 **Systematic reviews** Fernandez R, Griffiths R. *Water for wound cleansing*. Cochrane Database Syst Rev 2012, 2:CD003861.

Skin wounds – Disinfectant solution (First Aid)

Question (PICO)	In humans with a simple skin wound (P), is cleansing the wound with a disinfectant solution (I) compared to no cleansing with a disinfectant solution (C) effective to change tissue healing, functional recovery, pain, complications, time to resumption of usual activities, restoration to the pre-exposure condition, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "lacerations"] OR [mh "wounds,nonpenetrating"] OR laceration*:ti,ab,kw OR cut:ti,ab,kw OR cuts:ti,ab,kw OR graze*:ti,ab,kw OR "skin wound":ti,ab,kw OR "skin wounds":ti,ab,kw OR "nonpenetrating wound":ti,ab,kw OR "nonpenetrating wounds":ti,ab,kw 2. [mh "merbromin"] OR [mh "povidone-iodine"] OR [mh "saline solution,hypertonic"] OR [mh "ether"] OR Mercurochrome:ti,ab,kw OR Merbromine:ti,ab,kw OR ether:ti,ab,kw OR "povidone iodine":ti,ab,kw OR "povidone-iodine":ti,ab,kw OR "saline":ti,ab,kw

	3. cleans*:ti,ab,kw OR irrigat*:ti,ab,kw 4. 1-3 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "lacerations"[Mesh] OR "wounds,nonpenetrating"[Mesh] OR laceration*[TIAB] OR cut[TIAB] OR cuts[TIAB] OR graze*[TIAB] OR "skin wound"[TIAB] OR "skin wounds"[TIAB] OR "nonpenetrating wound"[TIAB] OR "nonpenetrating wounds"[TIAB] 2. Merbromin[Mesh] OR "povidone-iodine"[Mesh] OR "saline solution,hypertonic"[Mesh] OR ether[Mesh] OR Mercurochrome[TIAB] OR Merbromine[TIAB] OR OR ether[TIAB] OR OR "povidone iodine"[TIAB] OR "povidone-iodine"[TIAB] OR "saline"[TIAB] 3. cleans*[TIAB] OR irrigat*[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. laceration/exp OR blunt trauma/exp OR laceration*:ab,ti OR cut:ab,ti OR cuts:ab,ti OR graze*:ab,ti OR "skin wound":ab,ti OR "skin wounds":ab,ti OR "nonpenetrating wound":ab,ti OR "nonpenetrating wounds":ab,ti 2. merbromin/exp OR povidone iodine/exp OR sodium chloride/exp OR ether/exp OR merbromine:ab,ti OR ether:ab,ti OR 'povidone iodine':ab,ti OR 'povidone-iodine':ab,ti OR 'saline':ab,ti 3. cleans*:ab,ti OR irrigate*:ab,ti 4. 1-3 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	01 June 2015
In/Exclusion criteria	**Population:** Include: sick or injured people or healthy volunteers of all ages. Trials involving people of all ages with a wound (prior to suturing). A wound is defined as a break in the skin. **Intervention:** Include: disinfectant solutions that can be provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). The solutions should be used specifically for wound cleansing. Wound cleansing is defined as: "the use of fluids to remove loosely adherent debris and necrotic tissue from the wound surface". We included trials evaluating the use of a povidone-iodine solution, mercurochrome or ether compared with no cleaning or with another treatment. Exclude: saline solution (salt water solution), diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. We excluded trials that used pre-operative skin cleansing to prevent postoperative infections, trials that assessed the effectiveness of solutions as part of the operative procedure, trials that used a solution as a prophylactic treatment, and trials involving post-operative wound care. **Outcome**: Include: wound infection, proportion of wounds that healed, rate of wound healing, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched.

	An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomized controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Skin wounds – sterile compress/wound plaster/bandage (First Aid)

Question (PICO)	In humans with a simple skin wound (P), is covering the wound with a sterile compress/wound plaster/bandage (I) compared to not covering the wound with a sterile compress/wound plaster/bandage (C) effective to change tissue healing, functional recovery, pain, complications, time to resumption of usual activities, restoration to the pre-exposure condition, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "lacerations"] OR [mh "wounds,nonpenetrating"] OR laceration*:ti,ab,kw OR cut:ti,ab,kw OR cuts:ti,ab,kw OR graze*:ti,ab,kw OR "skin wound":ti,ab,kw OR "skin wounds":ti,ab,kw OR "nonpenetrating wound":ti,ab,kw OR "nonpenetrating wounds":ti,ab,kw 2. [mh "bandages"] OR "plaster":ti,ab,kw OR "compress":ti,ab,kw OR "bandage":ti,ab,kw OR dressing*:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy (limits: humans): 1. "lacerations"[Mesh] OR "wounds,nonpenetrating"[Mesh] OR laceration*[TIAB] OR cut[TIAB] OR cuts[TIAB] OR graze*[TIAB] OR "skin wound"[TIAB] OR "skin wounds"[TIAB] OR "nonpenetrating wound"[TIAB] OR "nonpenetrating wounds"[TIAB] 2. "bandages"[Mesh] OR "plaster"[TIAB] OR "compress"[TIAB] OR "bandage"[TIAB] OR dressing*[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy (limits: humans):

	1. laceration/exp OR blunt trauma/exp OR laceration*:ab,ti OR cut:ab,ti OR cuts:ab,ti OR graze*:ab,ti OR "skin wound":ab,ti OR "skin wounds":ab,ti OR "nonpenetrating wound":ab,ti OR "nonpenetrating wounds":ab,ti 2. 'bandages and dressings'/exp OR 'plaster':ab,ti OR 'compress':ab,ti OR 'bandage':ab,ti OR dressing*:ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	11 June 2015
In/Exclusion criteria	**Population:** Include: sick or injured people or healthy volunteers of all ages. Trials involving people of all ages with a wound. A wound is defined as a break in the skin. **Intervention:** Include: the use of a sterile compress/wound plaster/bandage Exclude: Interventions that do not take place during the acute phase which can be considered as aftercare. **Comparison:** Include: no use of a sterile compress/wound plaster/bandage **Outcome**: Include: wound infection, proportion of wounds that healed, rate of wound healing, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomized controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Skin wounds – Timing sterile compress/wound plaster (First Aid)

Question (PICO)	In humans with a simple skin wound (P), is covering the wound with a sterile compress/wound plaster at an early point (after cleansing) (I) compared to covering the wound with a sterile compress/wound plaster at a later point (after cleansing) (C) effective to change tissue healing, functional recovery, pain, complications, time to resumption of usual activities, restoration to the pre-exposure condition, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "lacerations"] OR [mh "wounds,nonpenetrating"] OR laceration*:ti,ab,kw OR cut:ti,ab,kw OR cuts:ti,ab,kw OR graze*:ti,ab,kw OR "skin wound":ti,ab,kw OR "skin wounds":ti,ab,kw OR "nonpenetrating wound":ti,ab,kw OR "nonpenetrating wounds":ti,ab,kw 2. "plaster":ti,ab,kw OR "compress":ti,ab,kw OR "tissue adhesive":ti,ab,kw OR "tissue adhesives":ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy (limits: humans): 1. "lacerations"[Mesh] OR "wounds,nonpenetrating"[Mesh] OR laceration*[TIAB] OR cut[TIAB] OR cuts[TIAB] OR graze*[TIAB] OR "skin wound"[TIAB] OR "skin wounds"[TIAB] OR "nonpenetrating wound"[TIAB] OR "nonpenetrating wounds"[TIAB] 2. "plaster"[TIAB] OR "compress"[TIAB] OR "tissue adhesive"[TIAB] OR "tissue adhesives"[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy (limits: humans): 1. laceration/exp OR blunt trauma/exp OR laceration*:ab,ti OR cut:ab,ti OR cuts:ab,ti OR graze*:ab,ti OR "skin wound":ab,ti OR "skin wounds":ab,ti OR "nonpenetrating wound":ab,ti OR "nonpenetrating wounds":ab,ti 2. 'plaster':ab,ti OR 'compress':ab,ti OR 'tissue adhesive':ab,ti OR 'tissue adhesives':ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	08 June 2015
In/Exclusion criteria	**Population:** Include: sick or injured people or healthy volunteers of all ages. Trials involving people of all ages with a wound. A wound is defined as a break in the skin. **Intervention:** Include: the use of a sterile compress/wound plaster/tissue adhesives at an early time point after cleansing/drying the wound Exclude: Interventions that do not take place during the acute phase which can be considered as aftercare. **Comparison:** Include: the use of a sterile compress/wound plaster/tissue adhesives at a later time point after cleansing/drying the wound **Outcome**: Include: wound infection, proportion of wounds that healed, rate of wound healing, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched.

	An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomized controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Skin wounds – Diabetes, swelling, lower extremity wound or contaminated wound (Risk factor)

Question (PICO)	In humans with a simple skin wound/wound with a foreign object (P) is diabetes/swelling/lower extremity wound or a contaminated wound (RF) a risk factor for wound infection, proportion of wounds that healed, rate of wound healing, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects) (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "lacerations"] OR [mh "wounds,nonpenetrating"] OR laceration*:ti,ab,kw OR cut:ti,ab,kw OR cuts:ti,ab,kw OR graze*:ti,ab,kw OR "skin wound":ti,ab,kw OR "skin wounds":ti,ab,kw OR "nonpenetrating wound":ti,ab,kw OR "nonpenetrating wounds":ti,ab,kw 2. [mh Edema] OR [mh Diabetes Mellitus] OR [mh lower extremity] OR [mh immobilization] OR Edema:ti,ab,kw OR Oedema:ti,ab,kw OR swelling:ti,ab,kw OR diabetes:ti,ab,kw OR lower extremity:ti,ab,kw OR lower extremities:ti,ab,kw OR lower limb:ti,ab,kw OR lower limbs:ti,ab,kw OR contaminated:ti,ab,kw OR infected:ti,ab,kw 3. [mh risk factors] OR "risk factor":ab,ti OR "risk factors":ab,ti 4. 1-3 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy (limits: humans): 1. "lacerations"[Mesh] OR "wounds,nonpenetrating"[Mesh] OR laceration*[TIAB] OR cut[TIAB] OR cuts[TIAB] OR graze*[TIAB] OR "skin wound"[TIAB] OR "skin wounds"[TIAB] OR "nonpenetrating wound"[TIAB] OR "nonpenetrating wounds"[TIAB] 2. "Edema"[Mesh] OR "Diabetes Mellitus"[Mesh] OR "lower extremity"[Mesh] OR "immobilization"[Mesh] OR "Edema"[TIAB] OR "Oedema"[TIAB] OR "swelling"[TIAB] OR

	"diabetes"[TIAB] OR "lower extremity"[TIAB] OR "lower extremities"[TIAB] OR "lower limb"[TIAB] OR "lower limbs"[TIAB] OR "contaminated"[TIAB] OR "infected"[TIAB] 3. "risk factors"[Mesh] OR "risk factor"[TIAB] OR "risk factors"[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy (limits: humans): 1. laceration/exp OR blunt trauma/exp OR laceration*:ab,ti OR cut:ab,ti OR cuts:ab,ti OR graze*:ab,ti OR "skin wound":ab,ti OR "skin wounds":ab,ti OR "nonpenetrating wound":ab,ti OR "nonpenetrating wounds":ab,ti 2. 'edema'/exp OR Diabetes Mellitus'/exp OR 'leg'/exp OR 'immobilization'/exp OR 'edema':ab,ti OR 'oedema':ab,ti OR 'swelling':ab,ti OR 'diabetes':ab,ti OR 'lower extremity':ab,ti OR 'lower extremities':ab,ti OR 'lower limb':ab,ti OR 'lower limbs':ab,ti OR 'contaminated':ab,ti OR 'infected':ab,ti 3. 'risk factors'/exp OR 'risk factor':ab,ti OR 'risk factors':ab,ti 4. 1-3 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	08 June 2015
In/Exclusion criteria	**Population:** Include: sick or injured people or healthy volunteers of all ages. Trials involving people of all ages with a wound. A wound is defined as a break in the skin. **Intervention:** Include: studies investigating the following risk factors were included: diabetes/swelling/lower extremity wound/contaminated wound. If analyzed in the included studies, other modifiable risk factors (relevant to lay people) were included. **Outcome**: Include: wound infection, proportion of wounds that healed, rate of wound healing, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomized controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Risk factors	Remarks
Hollander, 2001, USA	Observational: case-control study	5521 patients (at an emergency department) with traumatic lacerations which were infected	- History of diabetes mellitus - Bite wound - Injury with blunt object - Location on head/neck - Jagged wound margin	A multivariate logistic regression analysis was performed: adjusted factors were infiltrative anesthesia, use of scrub and irrigation for

		(n=194) or not (n=5327)	- Stellate shape - Visible contamination - Injury deeper than subcutaneous tissue - Alignment with skin tension lines - Foreign body wound	wound cleansing, use of subcutaneous or subcuticular sutures, use of oral antibiotics. Wound infection was defined as the presence of either a stitch abscess, cellulitis greater than 1 cm, or purulent drainage
Quinn, 2014, USA	Observational: case-control study	2663 patients (at an emergency department) with traumatic lacerations which were infected (n=69) or not (n=2594)	- Non-head and neck location - Diabetes - >5 cm length - Heavy or moderate contamination	

Synthesis of findings

Outcome	Risk factor	Effect Size	#studies, # participants	Reference
Risk of infection	History of diabetes mellitus vs no history of diabetes mellitus	Statistically significant: aOR: 6.74, 95%CI [1.7; 26.4] (p=0.006) £† *With harm for a history of diabetes*	1, 194 vs 5327	Hollander, 2001
	Diabetes vs no diabetes	Statistically significant: 5/69 vs 70/2594 § aOR: 3.1, 95%CI [1.2; 8.0] (p<0.05) *With harm for diabetes*	1, 69 vs 2594	Quinn, 2014
	Bite wound vs no bite wound	Not statistically significant aRR: 1.6, 95%CI [0.6; 3.5] (p>0.05) ¥£†	1, 194 vs 5327	Hollander, 2001
	Injury with blunt object vs no injury with blunt object	Statistically significant: aRR: 0.5, 95%CI [0.3; 0.7] (p<0.05) £† *With beneficiary effect for injury with blunt object*		
	Location on head/neck vs no location on head/neck	Statistically significant: aOR: 0.28, 95%CI [0.18; 0.45] (p<0.0001) £† *With beneficiary effect for location on head/neck*		
	Non-head and neck location vs head and no-neck location	Statistically significant: aOR: 2.5, 95%CI [1.4; 4.5] (p<0.05) £† *With beneficiary effect for head and no-neck location*	1, 69 vs 2594	Quinn, 2014
	Jagged wound margin vs no jagged wound margin	Statistically significant: aRR: 1.7, 95%CI [1.3; 2.4] (p<0.05) £† *With beneficiary effect of no jagged wound margin*	1, 194 vs 5327	Hollander, 2001
	Stellate shape vs no stellate shape	Not statistically significant: aRR: 1.6, 95%CI [0.95; 2.4] (p>0.05)¥ £†		

	Visible contamination vs no visible contamination	Statistically significant: aRR: 1.8, 95%CI [1.1; 2.8] (p<0.05) £† *With beneficiary effect of no visible contamination*		
	Injury deeper than subcutaneous tissue vs no injury deeper than subcutaneous tissue	Statistically significant: aRR: 1.6, 95%CI [1.01; 2.6] (p<0.05) £† *With beneficiary effect of no injury deeper than subcutaneous tissue*		
	Alignment with skin tension lines vs no alignment with skin tension lines	Not statistically significant: aRR: 0.95, 95%CI [0.6; 1.4] (p>0.05)¥ £†		
	Foreign body wound vs no foreign body wound	Statistically significant: aOR: 2.63, 95%CI [1.3; 5.2] (p=0.006) £† *With beneficiary effect of no foreign body wound*		
	Wound with (per 1mm)	Statistically significant: aOR: 1.05, 95%CI [1.02; 1.08] (p=0.0007) £† *With beneficiary effect of no wound (per 1 mm)*		
	Length >5 cm vs length ≤5 cm	Statistically significant: 13/69 vs 182/2578 § aOR: 2.4, 95%CI [1.4; 4.0] (p<0.05) *With beneficiary effect of length ≤5 cm*	1,69 vs 2578	Quinn,2014
	Lower extremity laceration vs no lower extremity laceration	Statistically significant: 21/64 vs 256/2535 § RR: 3.08, 95%CI [2.1; 4.5] (p<0.00001) *With beneficiary effect of no lower extremity laceration*	1,64 vs 2535	
	Heavy or moderate contamination vs no heavy/moderate contamination	Statistically significant: aOR: 1.9, 95%CI [1.04; 3.3] (p<0.00001) £† *With beneficiary effect of no heavy/moderate contamination*	1,69 vs 2594	
	Injury<12h vs injury>12h	Not statistically significant: 63/2176 vs 1/72 § RR: 2.08, 95%CI [0.29; 14.82] (p=0.46)	1, 2176 vs 72	

£ No information on (absolute) numbers available
¥ Imprecision (large variability of results)
§ Imprecision (limited sample size or low number of events)
† Imprecision (lack of data)

Quality of evidence

Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations
Hollander, 2001	no	no	no	no	
Quinn, 2014	no	no	no	no	

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Low number of events
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Conclusion	There is limited evidence with a harmful effect for the following risk factors: jagged wound margin, visible contamination, injury deeper than subcutaneous tissue, foreign body wound, length >5cm, lower extremity laceration, heavy/moderate contamination and diabetes. It was shown that these risk factors resulted in a statistically significant increased risk of wound infection (Hollander 2001, Quinn 2014). There is limited evidence with a protective effect for the following risk factors: injury with blunt object and location on head/neck. It was shown that injury with blunt object and location on head/neck resulted in a statistically significant decreased risk of wound infection (Hollander 2001). There is limited evidence showing no correlation between wound infection and the following risk factors: bite wound, stellate shape, alignment with skin tension and injury <12 hours. It was shown that bite wound, stellate shape, alignment with skin tension and injury <12 hours did not result in a statistically significant increased/decreased risk of wound infection compared to no bite wound, no stellate shape, no alignment with skin tension and injury >12 hours. Evidence is of very low quality and results cannot be considered precise due to low number of events.
Reference(s)	**Articles** Hollander JE, Singer AJ, Valentine SM, Shofer FS. *Risk factors for infection in patients with traumatic lacerations*. Acad Emerg Med 2001,8(7):716-20. Quinn JV, Polevoi SK, Kohn MA. *Traumatic lacerations: what are the risks for infection and has the 'golden period' of laceration care disappeared?* Emerg Med J 2014, 31(2):96-100.

Wound with a foreign object – Not removing object or immobilisation of object (Risk Factor)

Question (PICO)	In humans with a foreign object in the wound (P), is not removing this object or immobilisation of the object (RF) compared to removing/no immobilisation of this object (C) a risk factor for tissue healing, functional recovery, pain, complications, time to resumption of usual activities, restoration to the pre-exposure condition, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "lacerations"] OR [mh "wounds,nonpenetrating"] OR laceration*:ti,ab,kw OR cut:ti,ab,kw OR cuts:ti,ab,kw OR graze*:ti,ab,kw OR "skin wound":ti,ab,kw OR "skin wounds":ti,ab,kw OR "nonpenetrating wound":ti,ab,kw OR "nonpenetrating wounds":ti,ab,kw 2. [mh Edema] OR [mh Diabetes Mellitus] OR [mh lower extremity] OR [mh immobilization] OR Edema:ti,ab,kw OR Oedema:ti,ab,kw OR swelling:ti,ab,kw OR diabetes:ti,ab,kw OR lower extremity:ti,ab,kw OR lower extremities:ti,ab,kw OR lower limb:ti,ab,kw OR lower limbs:ti,ab,kw OR contaminated:ti,ab,kw OR infected:ti,ab,kw OR

	move:ti,ab,kw OR moving:ti,ab,kw OR remove:ti,ab,kw OR removing:ti,ab,kw OR immobilis*:ti,ab,kw OR immobiliz*:ti,ab,kw 3. [mh risk factors] OR "risk factor":ab,ti OR "risk factors":ab,ti 4. 1-3 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy (limits: humans): 1. "lacerations"[Mesh] OR "wounds,nonpenetrating"[Mesh] OR laceration*[TIAB] OR cut[TIAB] OR cuts[TIAB] OR graze*[TIAB] OR "skin wound"[TIAB] OR "skin wounds"[TIAB] OR "nonpenetrating wound"[TIAB] OR "nonpenetrating wounds"[TIAB] 2. "Edema"[Mesh] OR "Diabetes Mellitus"[Mesh] OR "lower extremity"[Mesh] OR "immobilization"[Mesh] OR "Edema"[TIAB] OR "Oedema"[TIAB] OR "swelling"[TIAB] OR "diabetes"[TIAB] OR "lower extremity"[TIAB] OR "lower extremities"[TIAB] OR "lower limb"[TIAB] OR "lower limbs"[TIAB] OR "contaminated"[TIAB] OR "infected"[TIAB] OR "move"[TIAB] OR "moving"[TIAB] OR "remove"[TIAB] OR "removing"[TIAB] OR immobilis*[TIAB] OR immobiliz*[TIAB] 3. "risk factors"[Mesh] OR "risk factor"[TIAB] OR "risk factors"[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy (limits: humans): 1. laceration/exp OR blunt trauma/exp OR laceration*:ab,ti OR cut:ab,ti OR cuts:ab,ti OR graze*:ab,ti OR "skin wound":ab,ti OR "skin wounds":ab,ti OR "nonpenetrating wound":ab,ti OR "nonpenetrating wounds":ab,ti 2. 'edema'/exp OR Diabetes Mellitus'/exp OR 'leg'/exp OR 'immobilization'/exp OR 'edema':ab,ti OR 'oedema':ab,ti OR 'swelling':ab,ti OR 'diabetes':ab,ti OR 'lower extremity':ab,ti OR 'lower extremities':ab,ti OR 'lower limb':ab,ti OR 'lower limbs':ab,ti OR 'contaminated':ab,ti OR 'infected':ab,ti OR 'move':ab,ti OR 'moving':ab,ti OR 'remove':ab,ti OR 'removing':ab,ti OR immobilis*:ab,ti OR immobiliz*:ab,ti 3. 'risk factors'/exp OR 'risk factor':ab,ti OR 'risk factors':ab,ti 4. 1-3 AND
Search date	08 June 2015
In/Exclusion criteria	**Population:** Include: sick or injured people or healthy volunteers of all ages. Trials involving people of all ages with a wound. A wound is defined as a break in the skin. **Risk factor:** Include: studies investigating the following risk factors were included: not removing the object/immobilization of the object. If analyzed in the included studies, other modifiable risk factors (relevant to lay people) were included. **Outcome**: Include: wound infection, proportion of wounds that healed, rate of wound healing, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomized controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Splinter – Removing with forceps or needle (First Aid)

Question (PICO)	In humans with a splinter (P), is removing it with a forceps or needle (I) effective compared to another treatment (C) to change tissue healing, functional recovery, pain, complications, time to resumption of usual activities, restoration to the pre-exposure condition, time to resolution of symptoms?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: Splinter:ti,ab,kw OR sliver:ti,ab,kw **MEDLINE** (via PubMed interface) using the following search strategy: 1. Splinter[TIAB] OR sliver[TIAB] 2. "surgical instruments"[Mesh] OR forceps[TIAB] OR needle[TIAB] OR remov*[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Splinter:ab,ti OR sliver:ab,ti 2. Forceps/exp OR needle/exp OR forceps:ab,ti OR needle:ab,ti 3. 1-2 AND
Search date	18 February 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available.

	An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Zipper injury – Cutting zipper crosswise (First Aid)

Question (PICO)	In humans with a wound due to a zipper (P), is cutting the zipper crosswise (I) effective compared to another treatment (C) to change tissue healing, functional recovery, pain, complications, time to resumption of usual activities, restoration to the pre-exposure condition, time to resolution of symptoms?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. zip*:ti,ab,kw 2. cut:ti,ab,kw OR cutting:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy (limits: humans): 1. "zip*"[TIAB] 2. "cut"[TIAB] OR "cutting"[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy (limits: humans): 1. zip*:ab,ti 2. cut:ab,ti OR cutting:ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	10 June 2015
In/Exclusion criteria	**Population:** Include: sick or injured people or healthy volunteers of all ages. Trials involving people of all ages with a zipper injury. **Intervention:** Include: studies investigating methods for zipper release (e.g. cutting zipper crosswise) that can be performed by lay people were included

	Outcome: Include: wound infection, proportion of wounds that healed, rate of wound healing, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomized controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Inoue, 2005, USA	Experimental: non-randomized controlled trial (within subjects design)	40 practitioners (20 males, 20 females) (paediatricians, residents, and medical students) who were instructed how to release the zipper	Intervention: "alternative" method: simply cutting the closed zipper teeth at any position to unzip the remaining zipper Control: "standard" method: cutting the median bar of the zipper	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Elapsed time to release the zipper (seconds)	cutting the closed zipper teeth at any position to unzip the remaining zipper versus cutting the median bar of the zipper	Males: Statistically significant: 9.0±5.3 vs 42.6±60.7 MD: -33.6±60.2 (p=0.022)	1, 20 vs 20 § (within subjects design)	Inoue, 2005
		Females: Statistically significant: 12.0±7.4 vs 109.1±112.4 MD: -97.1±108.5 (p=0.001)		

§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Inoue, 2005	Yes, no randomisation	no	no	no	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample size (n<400)
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is limited evidence in favour of cutting the closed zipper teeth at any position to unzip the remaining zipper. It was shown that this resulted in a statistically significant decreased elapsed time to release the zipper, compared to cutting the median bar of the zipper (Inoue, 2005). Evidence is of low quality and results cannot be considered precise due to the limited sample size.
Reference(s)	**Articles** Inoue N, Crook SC, Yamamoto LG. *Comparing 2 methods of emergent zipper release*. Am J Emerg Med 2005,23(4):480-2.

BURNS

Burns – Deroofing or aspiration (First Aid)

Question (PICO)	Among people with burns (P) is deroofing or aspiration (I) compared to leaving the blisters intact (C) effective to change tissue healing, functional recovery, pain, complications, time to resumption of usual activities, restoration to the pre-exposure condition, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "burns"] OR burn:ti,ab,kw OR burns:ti,ab,kw 2. [mh "blister"] OR blister:ti,ab,kw OR blisters:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for systematic reviews, experimental and observational studies using the following search strategy: 1. "burn"[TIAB] OR "burns"[TIAB] OR "burns"[Mesh] 2. "blister"[TIAB] OR "blisters"[TIAB] OR "blister"[Mesh] 3. 1-2 AND **Embase** (via Embase.com interface) for systematic reviews, experimental and observational studies using the following search strategy: 1. 'burn'/exp OR burn:ab,ti OR burns:ab,ti 2. 'blister'/exp OR blister:ab,ti OR blisters:ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	03 March 2015
In/Exclusion criteria	**General project-related eligibility criteria:** **Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available.

	Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies. **Language**: Include: English **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Swain 1987, UK	Experimental: non-randomized controlled trial	202 patients with 316 minor burns. Only thermal burns of the arms and legs that could be treated with paraffin gauze dressings were included.	Aspiration after 1 day vs deroofing after 1 day vs keeping blister intact for 10 days	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Number of blisters colonised with bacteria	Deroofing vs. keeping blister intact	Statistically significant: 78/102 vs 15/110 § RR: 5.61, 95%CI [3.46; 9.08] (p<0.00001) * *In favour of keeping intact*	1, 102 vs 110 blisters	Swain, 1987
Number of blisters colonised with *Staphylococcus aureus*		Statistically significant: 45/102 vs 2/110 § RR:24.26, 95%CI [6.04; 97.47] (p<0.00001) * *In favour of keeping intact*		
Number of blisters colonised with bacteria	Aspiration vs. keeping blister intact	Statistically significant: 73/104 vs 15/110 § RR:5.15, 95%CI [3.16; 8.37] (p<0.00001) * *In favour keeping intact*	1, 104 vs 110 blisters	
Number of blisters colonised with *Staphylococcus aureus*		Statistically significant: 19/104 vs 2/110 § RR:10.05, 95%CI [2.40; 42.08] (p=0.004) * *In favour of keeping intact*		

* The effect size and p-value was calculated by the reviewer using the Review Manager Software
§ Imprecision (low number of events)

Quality of evidence:

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Swain 1987	Yes	Yes	No	No	No randomization; not clear if one person's blisters were all treated in the same way

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Low number of events
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is limited evidence from 1 experimental study in favour of keeping a blister intact: It was shown in one study that keeping a blister intact resulted in a statistically significant decrease of bacteria/*Staphylococcus aureus* colonisation, compared to aspirating of deroofing a blister (Swain 1987). Evidence is of low quality and results cannot be considered precise due to limited sample size.
Reference(s)	**Articles** Swain AH, Azadian BS, Wakeley CJ, Shakespeare PG. *Management of blisters in minor burns.* Br Med J (Clin Res Ed). 1987, 295(6591):181

Burns – Ice (First Aid)

Question (PICO)	Among adults and children with thermal injuries (P), does cooling with ice (I), compared with not cooling with ice (C), change pain, complications, wound healing, need for advanced medical care, patient satisfaction, rates of fasciotomy, depth or breadth of burn (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "burns"] OR burn:ti,ab,kw OR burns:ti,ab,kw 2. [mh ice] OR ice:ti,ab,kw OR [mh cryotherapy] OR cryotherapy:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "burn"[TIAB] OR "burns"[TIAB] OR "burns"[Mesh] 2. Ice[Mesh] OR ice[TIAB] OR cryotherapy[Mesh] OR cryotherapy[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'burn'/exp OR burn:ab,ti OR burns:ab,ti 2. Ice/exp OR ice:ab,ti OR cryotherapy/exp OR cryotherapy:ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	03 June 2015
In/Exclusion criteria	**Population**: Include: people with acute burn injuries. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Comparison:** Studies comparing the use of ice with no treatment of with cold water. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers.

	Design: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Cuttle, 2009, Australia	Observational: Cohort study	459 children (aged 2 months -14.5 years) presenting to hospital burns centre with new burns. Patients had a mean burn BSA of 2.8±4.2% with superficial to mid-depth partial-thickness burns. Different first-aid measures were used: nothing (n=40), cold water (n=289), cold water + others (n=60), Ice (16), Cream (n=8), cold compress (n=7), others (n=14)	1. No treatment 2. Cold water 3. Cold water + others 4. Ice 5. Cream 6. Cold compress 7. Others [only data on ice, cold water and no treatment were extracted]	BSA = body surface area

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Grafted	Ice vs no treatment	Not statistically significant: 4/16 vs 5/40 § OR: 2.33, 95%CI [0.54; 10.14] (p=0.26) *¥	1, 16 vs 40	Cuttle, 2009
	Ice vs cold water	Statistically significant: 4/16 vs 21/289 § OR: 4.25, 95%CI [1.26; 14.35] (p=0.02) * *In favour of cold water*	1, 16 vs 289	
Scar management	Ice vs no treatment	Not statistically significant: 5/16 vs 8/40 § OR: 1.82, 95%CI [0.49; 6.74] (p=0.37) *¥	1, 16 vs 40	
	Ice vs cold water	Not statistically significant: 5/16 vs 51/289 § OR: 2.12, 95%CI [0.71; 6.37] (p=0.18) *¥	1, 16 vs 289	
Days to re-epithelialize	Ice vs no treatment	Not statistically significant: 13.5±7.9 vs 15.6±12.8 MD: -2.10, 95%CI [-7.64; 3.44] (p=0.46) *¥	1, 16 vs 40 §	
	Ice vs cold water	Not statistically significant:	1, 16 vs 289 §	

		13.5±7.9 vs 12.2±8.9 MD: 1.30, 95%CI [-2.70; 5.30] (p=0.52) *¥		
Number of visits	Ice vs no treatment	Not statistically significant: 6±5.7 vs 5±5.1 MD: 1.00, 95%CI [-2.21; 4.21] (p=0.54) *¥	1, 16 vs 40 §	
	Ice vs cold water	Not statistically significant: 6±5.7 vs 5±4.4 MD: 1.00, 95%CI [-1.84; 3.84] (p=0.54) *¥	1, 16 vs 289 §	

Mean ± SD (unless otherwise indicated)
* Calculations done by the reviewer(s) using Review Manager software
§ Imprecision (limited sample size or low number of events)
¥ Imprecision (large variability of results)

Quality of evidence

Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations
Cuttle, 2009	No	No	Unclear	No	

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Limited sample size or low number of events/large variability of the results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Conclusion	**Ice vs no treatment** There is limited evidence from 1 experimental study neither in favour of the intervention nor the control. A statistically significant decrease of the need for grafts or scar management, or a decrease of days the re-epithelialize or number of visits, using ice compared to no treatment, could not be demonstrated (Cuttle 2009). Evidence is of very low quality and results of this study are imprecise due to limited sample size and/or large variability of results. **Ice vs cold water** There is limited evidence from 1 experimental study in favour of cold water. It was shown that ice resulted in a statistically significant increase in the need of grafts, compared to cold water (Cuttle 2009). However, a statistically significant decrease of the need for scar management, or a decrease of days the re-epithelialize or number of visits, using ice compared to no treatment, could not be demonstrated. Evidence is of very low quality and results of this study are imprecise due to limited sample size and/or large variability of results.
Reference(s)	**Articles** Cuttle L, Kravchuck O, Wallis B, Kimble RM. *An Audit of First-Aid Treatment of Pediatric Burns Patients and Their Clinical Outcome.* J Burn Care Res 2009, 30:1028-1034

Burns – Plastic foil (First Aid)

Question (PICO)	In humans with burns (P), is wrapping the burn wound with plastic foil (I) compared to not doing this (C) effective to change tissue healing, functional recovery, pain, complications, time to resumption of usual activities, restoration to the pre-exposure condition, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh burns] OR burn:ti,ab,kw OR burns:ti,ab,kw 2. ((plastic:ti,ab,kw OR cling:ti,ab,kw OR food:ti,ab,kw OR polyethylene:ti,ab,kw OR Glad:ti,ab,kw OR Saran:ti,ab,kw) AND (foil:ti,ab,kw OR wrap:ti,ab,kw OR film:ti,ab,kw)) OR clingfilm:ti,ab,kw OR clingwrap:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. burn[TIAB] OR burns[TIAB] OR burns[Mesh] 2. ((Plastic[TIAB] OR cling[TIAB] OR food[TIAB] OR polyethylene[TIAB] OR Glad[TIAB] OR Saran[TIAB]) AND (foil[TIAB] OR wrap[TIAB] OR film[TIAB])) OR clingfilm[TIAB] OR clingwrap[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. burn/exp OR burns:ab,ti OR burn:ab,ti 2. ((plastic:ab,ti OR cling:ab,ti OR food:ab,ti OR polyethylene:ab,ti OR Glad:ab,ti OR Saran:ab,ti) AND (foil:ab,ti OR wrap:ab,ti OR film:ab,ti)) OR clingfilm:ab,ti OR clingwrap:ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	23 July 2015
In/Exclusion criteria	**Population**: Include: people with burns **Intervention**: Include: domestic plastic foil. Exclude: polyurethane foil. **Comparison**: Include: no treatment or other types of burn dressings. Exclude: topical treatments such as ointments, honey. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values.

	Language: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Burns – Vaseline (First Aid)

Question (PICO)	In people with burns (P), does using vaseline (I), compared to not using vaseline (C), influence survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of the symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "burns"] OR burn*:ti,ab,kw 2. [mh "petrolatum"] OR petrolatum*:ti,ab,kw OR (paraffin NEXT/1 jell*):ti,ab,kw OR vaselin*:ti,ab,kw OR cosmolin*:ti,ab,kw OR saxolin*:ti,ab,kw OR (petroleum NEXT/1 jell*):ti,ab,kw 3. #1 AND #2 **MEDLINE** (via PubMed interface) for guidelines, systematic reviews, experimental and observational studies using the following search strategy: 1. "burns"[MeSH] OR burn*[TIAB] 2. "petrolatum"[MeSH] OR petrolatum*[TIAB] OR paraffin jell*[TIAB] OR vaselin*[TIAB] OR cosmolin*[TIAB] OR saxolin*[TIAB] OR petroleum jell*[TIAB] 3. #1 AND #2 **Embase** (via Embase.com interface) using the following search strategy: 1. 'burns'/exp OR burn*:ab,ti 2. 'petrolatum'/exp OR petrolatum:ab,ti OR (paraffin NEXT/1 jell*):ab,ti OR vaselin*:ab,ti OR cosmolin*:ab,ti OR saxolin*:ab,ti OR (petroleum NEXT/1 jell*):ab,ti 3. #1 AND #2 Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	17th May 2016

In/Exclusion criteria	**Population:** Include: People with superficial partial thickness burns Exclude: people with full thickness burns. **Intervention:** Include: Topical use of vaseline Exclude: Commercially available sterilized vaseline gauzes. **Comparison:** Include: Standard acute burn management/no burn management. **Outcome:** Include: Functional recovery, time to recovery, prevalence of adverse events. **Study design:** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: observational studies if intervention is already included in experimental studies, case series, cross-sectional studies, animal studies, ex vivo or in vitro studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English, French, German, Dutch. **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Genuino, 2014, The Philippines	Experimental: Randomised controlled trial	Otherwise healthy adults, presenting consecutively at the Burn center of the Philippine general hospital, with superficial partial thickness burns, within 24 h and without receiving prior cooling or treatment. Treatment group (n=19): 30.8±9.5 years, 17 males and 2 females, % total body surface area affected: 2.4±1.1% Control group (n=19): 32.3±9.6 years, 17 males and 2 females, % total body surface affected: 3.3±2.0%	Treatment group: Initial cleansing of the wound, followed by a 1 mm layer of Vaseline, without further covering, and reapplied as needed Control group: Initial cleansing of the wound, followed by the standard treatment, consisting of a fine mesh gauze with a 2 mm of silver sulfadiazine, covered with moist gauze, an upper layer of dry gauze and wrapped with rolled gauze. All patients received an oral analgesic treatment of 50 mg tramadol every 8 h.	A power analysis assuming a mean time to re-epithelialisation of 5 days revealed a power of 0.836 for sample sizes of 20 participants. Assuming a drop-out of 20%, 25 participants were aimed to be recruited per group, though in practice this turned out to be 26 vs 24

Synthesis of findings

Outcome	Comparison/Risk factor	Effect Size	#studies, # participants	Reference
Time to re-epithelialisation (days)	Vaseline vs silver sulfadiazine covered with a gauze	Not statistically significant: 6.2±2.8 vs 7.8±2.1 MD: 1.63, 95%CI [-0.01;3.26] (p=0.05)	1, 19 vs 19 §	Genuino, 2014
		Statistically significant: 5 [4;8] vs 7 [7;10] (median [IQR])		

		Median difference: -2 (p=0.03) *In favour of vaseline*		
Infection rate		Not estimable: 0/19 vs 0/19		
Allergic contact dermatitis		Not estimable: 0/19 vs 0/19		
Ease of dressing removal (3-point Likert scale)		Statistically significant: 1 [1;1] vs 1.5 [1;2] (median [IQR]) Median difference: -0.5 (p=0.002) *In favour of vaseline*		
Adherence to the wound (4-point Likert scale)		Statistically significant: 1 [1;1] vs 2 [1.5;2] (median [IQR]) Median difference: -1 (p=0.000) *In favour of vaseline*		
Pain during dressing removal (VAS 1-10)		Not statistically significant: 4.22±1.13 vs 4.88±1.62 MD: 0.66, 95%CI [-0.26;1.58] (p=0.156)		
Pain during wound dressing (VAS 1-10)		Not statistically significant: 3.50±1.00 vs 3.80±1.32 MD: 0.30, 95%CI [-0.46;1.07] (p=0.432)		
Time to change wound dressing (6-point Likert scale)		Statistically significant: 1 [1;1] vs 2 [2;2] (median [IQR]) Median difference: -1 (p=0.000) *In favour of vaseline*		
Number of dressing changes (3-point Likert scale)		Not statistically significant: 1 [1;1] vs 1 [1;1] (median [IQR]) Median difference: 0 (p=0.84)		

Mean ± SD (unless otherwise indicated)

§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Genuino, 2014	No, randomisation happened via a computer-generated table, although the fact that the amount of participants in each group differed by 1 volunteer suggests that the principal investigator has manually allocated 1 volunteer to correct for	No, principal investigator was blinded for the primary outcomes and patients were impossible to blind due to the nature of the interventions	No, loss to follow up of approximately 20% that was anticipated and accounted for (burn victims living too far from the hospital to return for treatment)	No, all pre-defined outcomes were reported	No

	unequal drop-out in both groups				

Level of evidence

	High [A]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Moderate [B]**	

Conclusion	There is limited evidence in favour of application of vaseline: It was shown that vaseline application resulted in a statistically significant decrease of time to re-epithelialisation, adherence to the wound, time to change the dressing, and a statistically significant increase in ease of dressing removal compared to silver sulfadiazine covered with a gauze. In addition, a statistically significant decrease in pain during dressing application, pain during dressing removal and amount of dressing changes using vaseline compared to silver sulfadiazine covered with a gauze, could not be demonstrated. Evidence is of moderate quality and results of this study are imprecise due to a limited sample size.
Reference(s)	**Articles** Genuino GA, Baluyut-Angeles KV, Espiritu AP, Lapitan MC, Buckley BS. *Topical petrolatum gel alone versus topical silver sulfadiazine with standard gauze dressings for the treatment of superficial partial thickness burns in adults: a randomized controlled trial.* Burns. 2014, 40(7):1267-73.

Burns – Honey (First Aid)

Question (PICO)	In people with burns (P), is treating the burn with honey (I) effective for survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of the symptoms (O) compared to alternative treatment options (C)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "burns"] OR burn*:ti,ab,kw 2. [mh "honey"] OR honey*:ti,ab,kw 3. #1 AND #2
Search date	1 February 2016
In/Exclusion criteria	**Population:** Include: People with burns. **Intervention:** Include: Treatment with honey. Exclude: Any other type of acute burn management. **Comparison:** Include: Any other type of acute burn management, no burn management. **Outcome:** Include: Functional recovery, time to recovery, prevalence of adverse events. **Study design:** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available.

	Exclude: observational studies if intervention is already included in experimental studies, case series, cross-sectional studies, animal studies, ex vivo or in vitro studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English, French, German, Dutch. **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Jull, 2015, New Zealand	Systematic review on the effects of honey as treatment for wounds	Experimental: 2 RCT's, 992 patients with burn wounds, divided into 6 treatment groups	Honey vs conventional dressings (polyurethane film, paraffin gauze, sterile linen dressing, antimicrobial gauze or left exposed) [Only data for the acute treatment of burns was extracted]	1 study tested honey vs polyurethane film (46 vs 46) the other honey (450) vs polyurethane film (90), paraffin gauze (90), sterile linen dressing (90), antimicrobial gauze (90) or left exposed (90)
		Experimental: 6 RCT's, 462 patients with burn wounds, divided into two treatment groups	honey vs silver sulfadiazine [Only data for the acute treatment of burns was extracted]	
		Experimental: 2 RCT's, 164 patients with burn wounds, divided into three treatment groups	honey vs atypical dressings (amniotic membranes or boiled potato peels) [Only data for the acute treatment of burns was extracted]	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Time to healing (days)	Honey vs conventional dressings	Statistically significant: MD: -4.68, 95%CI [-5.09;-4.28] (p<0.00001) *In favour of honey*	2, 496 vs 496	Jull, 2015
Occurrence of adverse events		Not statistically significant: 37/496 vs 102/496 RR: 0.56, 95%CI [0.15;2.06] ¥ (p=0.38)		
Negative swab at day 7-8		Statistically significant: 38/46 vs 29/46 RR: 1.31, 95%CI [1.01;1.7] (p<0.00001) *In favour of honey*	1, 46 vs 46 §	
Time to healing (days)	Honey vs silver sulfadiazine	Statistically significant: MD: -5.12, 95%CI [-9.51;-0.73] (p=0.022) *In favour of honey*	4, 164 vs 168 §	
Proportion of burns fully healed		Not statistically significant: 229/229 vs 233/233	6, 229 vs 233 §	

		RR: 1.00, 95%CI [0.98;1.02] (p=1.0)		
Occurrence of adverse events		Statistically significant: 22/204 vs 86/208 RR: 0.29, 95%CI [0.2;0.42] (p<0.00001) *In favour of honey*	5, 204 vs 208 §	
Negative swab at day 7-8		Statistically significant: 175/204 vs 49/208 RR: 3.92, 95%CI [1.32;11.63] (p=0.014) *In favour of honey*	5, 204 vs 208 §	
Time to healing (days)	Honey vs amniotic membranes	Statistically significant: 9.4±2.52 vs 17.5±6.66 MD: -8.1, 95%CI [-10.88;-5.32] (p<0.00001) *In favour of honey*	1, 40 vs 24 §	
	Honey vs boiled potato peels	Statistically significant: 10.4±2.2 vs 16.2±2.3 MD: -5.8 , 95%CI [-6.68;-4.92] (p<0.00001) *In favour of honey*	1, 50 vs 50 §	

¥ Imprecision (large variability of results)
§ Imprecision (limited sample size)

Level of evidence

Treatment with honey vs conventional dressings

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See Cochrane review
Imprecision	-1	Limited sample size for 1/3 outcomes, large variability for another 1/3 outcomes
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Moderate [B]**	

Treatment with honey vs silver sulfadiazine

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See Cochrane review
Imprecision	-1	Limited sample sizes for all outcomes tested
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Moderate [B]**	

Treatment with honey vs alternative dressings

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See Cochrane review
Imprecision	-1	Limited sample sizes for all outcomes tested
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Moderate [B]**	

Conclusion	There is limited evidence in favour of using honey over conventional dressings: It was shown that treatment with honey resulted in a statistically significant decrease in time to healing, compared to treatment with conventional dressings. A statistically significant increase of adverse events, using honey compared to conventional dressings, could not be demonstrated. On the other hand, it was shown that honey resulted in a statistically significant decrease of negative swabs at day 7-8, compared to conventional dressings (Jull 2015). Evidence is of moderate quality and results cannot be considered precise due to limited sample size or large variability of results. There is limited evidence in favour of using honey over silver sulfadiazine: It was shown that treatment with honey resulted in a statistically significant decrease in time to healing and adverse events, compared to treatment with silver sulfadiazine. It was shown that treatment with honey resulted in a statistically significant increase of negative swabs at day 7-8, compared to treatment with silver sulfadiazine. On the other hand, a statistically significant increase of the proportion of fully healed burns, using honey compared to silver sulfadiazine, could not be demonstrated (Jull 2015). Evidence is of moderate quality and results cannot be considered precise due to limited sample size. There is limited evidence in favour of using honey over alternative dressings: It was shown that treatment with honey resulted in a statistically significant decrease in time to healing, compared to treatment with amniotic membranes or boiled potato peels. Evidence is of moderate quality and results cannot be considered precise due to limited sample size.
Reference(s)	**Systematic review:** Jull AB, Cullum N, Dumville JC, Westby MJ, Deshpande S, Walker N. *Honey as a topical treatment for wounds (Review)*. Cochrane Database Syst Rev. 2015 Mar 6;3:CD005083.

Burns – Papaya, sugar or fatty acids (First Aid)

Question (PICO)	In people with burns (P), is treatment with papaya, sugar or fatty acids (I) effective for survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of the symptoms (O) compared to no treatment or alternative treatments (C)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "burns"] OR burn*:ti,ab,kw 2. [mh "sucrose"] OR sugar*:ti,ab,kw OR sucr*:ti,ab,kw OR [mh "carica"] OR carica*:ti,ab,kw OR papaya*:ti,ab,kw OR [mh "fatty acids"] OR (fatty NEXT acid*):ti,ab,kw 3. #1 AND #2 **MEDLINE** (via PubMed interface) for systematic reviews, experimental and observational studies using the following search strategy: 1. burns[MeSH] OR burn*[TIAB] 2. sucrose[MeSH] OR sugar*[TIAB] OR sucr*[TIAB] OR carica[MeSH] OR carica*[TIAB] OR papaya*[TIAB] OR (((fatty acids[MeSH] OR fatty acid*[TIAB]) AND (therapy[MeSH] OR therap*[TIAB] OR treat*[TIAB])) NOT (metabolism[MeSH] OR metabol*[TIAB] OR adipocytes[MeSH] OR adipo*[TIAB])) 3. #1 AND #2 **Embase** (via Embase.com interface), for systematic reviews, experimental and observational studies using the following search strategy: 1. 'burns'/exp OR burn*:ab,ti

	2. 'sucrose'/exp OR sugar*:ab,ti OR sucr*:ab,ti OR 'carica'/exp OR carica*:ab,ti OR papaya*:ab,ti OR ((('fatty acid'/exp OR (fatty NEXT/1 acid*):ab,ti) AND ('therapy'/exp OR therap*:ab,ti OR treat*:ab,ti)) NOT ('metabolism'/exp OR metabol*:ab,ti OR 'adipocyte'/exp OR adipo*:ab,ti)) 3. #1 AND #2 Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	10 February 2016
In/Exclusion criteria	**Population:** Include: People with burns. **Intervention:** Include: Treatment with sugar, papaya or fatty acids. Exclude: Any other type of acute burn management. **Comparison:** Include: Any other type of acute burn management, no burn management. **Outcome:** Include: Functional recovery, time to recovery, prevalence of adverse events. **Study design:** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: observational studies if intervention is already included in experimental studies, case series, cross-sectional studies, animal studies, ex vivo or in vitro studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English, French, German, Dutch. **Publication year**: Include: all years.

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Jelenko, 1976, USA	Experimental: Non-randomized controlled trial	60 patients with burns, receiving standard treatment (resuscitation, management of pulmonary injury, topical neospirin for the first 3 days, followed by silvadine, debridement in a Hubbard twice a day, 6 days a week), 31 in the treatment group (27 males, aged 35.77±2.96 years) and 29 in the control group (44.48±2.7 years).	The control group was compared to the treatment group, receiving a single application of ±25 mg/kg topical application of ethyl linoleate with appropriate antioxidants (hELate)	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Narcotic requirement (% of hospital stay)	hELate treated vs not hELate treated	Statistically significant: 35.3±5.4 vs 56.4±5.1 MD: -21.1, 95%CI [-35.66;-6.54] (p=0.0063) * *With beneficial effect for hELate treatment*	1, 31 vs 29 §	Jelenko, 1976
Hospital stay (days)		Not statistically significant: 37.23±4.25 vs 47.59±6.07 MD:-10.36, 95%CI [-24.88;4.16] (p=0.163) *		

Appearance of epithelium (days)		Statistically significant: 7.82±1.34 vs 15.92±1.53 MD: -8.1, 95%CI [-12.09;-4.11] (p=0.0002) * *With beneficial effect for hELate treatment*		
Appearance of normal pigment		Statistically significant: 27/31 vs 0/29 § RR: 51.56, 95%CI [3.29;808.34] (p=0.005) * *With beneficial effect for hELate treatment*		
Appearance of normal hair		Statistically significant: 26/31 vs 0/29 § RR: 49.69, 95%CI [3.17;779.69] * (p=0.005) *With beneficial effect for hELate treatment*		
Amount of positive cultures (urine, sputum, blood, surface)		Not statistically significant: 11/124 vs 12/117 § RR: 0.86, 95%CI [0.4;1.88] (p=0.71) *¥		
Patients requiring grafts		Statistically significant: 9/31 vs 22/29 § RR: 0.38, 95%CI [0.21;0.69] (p=0.001) * *With beneficial effect for hELate treatment*		
Patients requiring reconstructions		Not statistically significant: 2/31 vs 5/29 § RR: 0.37, 95%CI [0.08;1.78] (p=0.22) *¥		
Mortality		Not statistically significant: 5/31 vs 6/29 § RR: 0.78, 95%CI [0.27;2.28] (p=0.65) *¥		

Mean ± SEM

* Calculations done by the reviewer using Review Manager software

¥ Imprecision (large variability of results)

§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Jelenko, 1976	Unclear, not mentioned by the author	Unclear, not mentioned by the author	No	No	Treatment and control group are heterogeneous concerning age (higher in control group) and body surface burned (higher in treatment group). This is however considered no problem by the authors, as the "Phillips" index is not different, which takes into account that patients of advanced age and patients with a lesser burn surface have respectively a higher and lower mortality from burns. This however raises the question whether this is also true for wound healing. Furthermore, a significantly larger amount of

					treatment patients fulfil criteria of post burn respiratory injury.

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample size and large variability of results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	Concerning the use of sugar for the treatment of burns, no relevant studies were identified using the above search strategy and criteria. Concerning the use of papaya for the treatment of burns, no relevant studies were identified using the above search strategy and criteria. Concerning the use of fatty acids for the treatment of burns, there is limited evidence in favour of ethyl linoleate. It was shown that adjuvant topical application of ethyl linoleate resulted in a statistically significant decrease in narcotic requirement, time to appearance of epithelium, the appearance of normal pigment and hair and the amount of patients requiring grafts compared to standard burn management (Jelenko, 1976). On the other hand, a statistically significant decrease in length of hospital stay, amount of positive cultures, amount of patients requiring reconstructions and mortality, using adjuvant ethyl linoleate compared to standard burn management, could not be demonstrated (Jelenko, 1976). Evidence is of low quality and results cannot be considered precise due to limited sample size and large variability of results.
Reference(s)	**Articles** Jelenko C 3rd, McKinley JC. *Studies in burns: XV. Use of a topical lipid in treating human burns.* Am Surg. 1976 Nov;42(11):838-48.

Burns – Risk factors

Question (PICO)	In humans with burns (P) is depth of the burn, burned surface, age of the victim, location of burn or cause of the burn (RF) a risk factor for death, infection, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects) (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh burns] OR burn:ti,ab,kw OR burns:ti,ab,kw 2. Depth:ti,ab,kw OR surface:ti,ab,kw OR location:ti,ab,kw OR body part*:ti,ab,kw OR (age:ti,ab,kw AND victim:ti,ab,kw) OR cause:ti,ab,kw 3. [mh "risk factors"] OR risk factor*:ti,ab,kw 4. [mh Mortality] OR mortality:ti,ab,kw OR [mh cicatrix] OR scar*:ti,ab,kw OR function*:ti,ab,kw OR [mh infection] OR infect*:ti,ab,kw 5. 1-4 AND

	MEDLINE (via PubMed interface) for experimental and observational studies using the following search strategy: 1. burns[Mesh] OR burn[TIAB] OR burns[TIAB] 2. depth[TIAB] OR surface[TIAB] OR location[TIAB] OR body part*[TIAB] OR (age[TIAB] AND victim[TIAB]) OR cause[TIAB] 3. "risk factors"[Mesh] OR risk factor*[TIAB] 4. Mortality[Mesh] OR mortality[TIAB] OR cicatrix[Mesh] OR scar*[TIAB] OR function*[TIAB] OR infection[Mesh] OR infect*[TIAB] 5. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Burn/exp OR burn:ab,ti OR burns:ab,ti 2. Depth:ab,ti OR surface:ab,ti OR 'body region'/exp OR location:ab,ti OR body part*:ab,ti OR age/exp OR (age NEXT/4 victim*):ab,ti OR cause:ab,ti 3. 'risk factor'/exp OR 'risk factor':ab,ti OR 'risk factors':ab,ti 4. Mortality/exp OR mortality:ab,ti OR scar/exp OR scar*:ab,ti OR function*:ab,ti OR infection/exp OR infect*:ab,ti 5. 1-4 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	31 July 2015
In/Exclusion criteria	**Population**: Include: children and adults with accidental burns who are otherwise healthy. Exclude: people with self-inflicted burn injury, burn victims with HIV, diabetes,… **Risk factor**: Include: risk factors such as depth of the burn, location of the burn, percentage of body surface burned, age of the victim (preferably <5 years or >60 years compared with ages in between, if these categories , cause of burn, body mass index (BMI), inhalation injury. Exclude: hospital related risk factors, such as ventilation, catheters, bacterial or viral infection, biochemical factors. **Outcome**: Include: mortality, infection, scarring, function loss, sepsis, multiple organ failure, length of hospital stay. Exclude: psychosocial status. **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An observational study: inclusion in case of one of the following study types: prospective cohort study: if criteria for enrollment are described, if approved by ethical committee or if followed from admission to discharge; case-control study: if number of patients in each group is mentioned in methods section; controlled before and after study or controlled interrupted time series, and the data are available. Exclude: retrospective cohort studies, case series, cross-sectional studies, animal studies, *ex vivo* or *in vitro* studies. **Language**: Include: English **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Risk factors	Remarks
Attia, 2000, Egypt	Observational: cohort study	533 burn patients admitted to the Alexandria Main University Hospital Burns Unit from January – December 1997.	- Age: <10, >40 years vs 10-40 years - Sex: male vs female - TSAB (total surface area burnt): 40%, 100% vs 20% - Agent: Flame vs non-flame - Depth: Superficial vs deep	Data were collected by questionnaire-interview with patients using a pre-planned specially designed questionnaire. Data were

			- Degree: 1st and 2nd vs 2nd, 3rd, 2nd and 3rd - Inhalation vs no inhalation	collected on admission and updated on discharge.
Cumming, 2001, USA	Observational: cohort study	85 burn victims, median age 35 years, 64 males, 21 females, admitted to the burn unit at Parkland Memorial Hospital between July 1, 1998 and June 30, 1999 with ≥20% total body surface area (TBSA) burns (range from 20-96%) were enrolled. Those with more severe burns, in whom the initial decision was for comfort care, were excluded.	- Sex: male vs female - Inhalation vs no inhalation - Age - Percent TBSA	Daily data was recorded with information to assess multiple organ dysfunction score (MODS) and sepsis status.
Fazeli, 2014, Iran	Observational: cohort study	540 burn patients who were admitted to the burn ward of the Imam Khomeini Hospital between March 20, 2011 and March 21, 2012. Patients were followed from admission to discharge.	- Age: <15 vs 15-60 and >60 years - Sex: Male vs female - % TBSA - Cause of burn: other causes vs flame [Crude and adjusted odds ratios are presented, only adjusted odds ratios were extracted]	Total body surface area (TBSA) burns were calculated using the rule of nines or the Lund-Browder diagram. A trained person was responsible for filling the forms by asking the victims or their attendants the designed questions.
Fitzwater, 2003, USA	Observational: cohort study	175 burn patients, aged 16 years or older (median age 40 years), 82 males and 93 females, admitted to the burn unit at Parkland Memorial Hospital between July 1, 1998 and June 30, 2000 with ≥20% total body surface area (TBSA) burns (median 32%) were enrolled. Those with more severe burns, in whom the initial decision was for comfort care only and were not resuscitated, were excluded.	- Age: <50 vs ≥50 years - Sex: male vs female - TSAB: full-thickness burn ≥30% TBSA vs <30% - Inhalation injury vs no inhalation injury	Daily data was recorded with information to assess MOD score and sepsis status.
Tarim, 2013, Turkey	Observational: case-control study	Patients who were hospitalized in Adana burn unit of Baskent University between January 2000 and June 2011. Patients who underwent amputation (n=44) were compared	Cause of burn: electrical vs other causes (scald, flame, chemical, contact)	

		with patients without amputations (n=1100)		

Synthesis of findings

Outcome	Risk factor	Effect Size	#studies, # participants	Reference
Age				
Mortality	<10 vs 10-20 vs 21-40 vs >40	Statistically significant: 23/131 vs 46/120 vs 66/211 vs 41/71 § (p<0.05) £† *with harm for older age*	1, 131 vs 120 vs 211 vs 71	Attia, 2000
Death risk (%)	15-60 vs <15 years	Not statistically significant: 29.4 vs 5.7 aOR: 0.24, 95%CI [0.03; 2.93] (p=0.18) ¥	1, 395 § (exact numbers in each group not mentioned)	Fazeli, 2014
	>60 vs <15 years	Statistically significant: 42.4 vs 5.7 aOR: 19.74, 95%CI [1.37; 284.41] (p=0.03) *with harm for >60 years*		
MODS ≥6	Age	Statistically significant: aOR: 1.03, 95%CI [1.01; 1.07] (p<0.05) *with harm for older age*	1, 24 § (no mention of different groups)	Cummings, 2001
	≥50 years vs <50 years	Statistically significant: aOR: 4.4, 95%CI [1.9; 10.6] (p<0.05) *with harm for ≥50 years*	1, 128 § (exact numbers in each group not mentioned)	Fitzwater, 2003
Sex				
Mortality	Male vs female	Statistically significant: 48/266 vs 128/267 § (p<0.05) £† *with harm for female sex*	1, 266 vs 267	Attia, 2000
Death risk (%)	Female vs male	Statistically significant: 39.1 vs 14.2 aOR: 9.02, 95%CI [1.35; 60.01] (p=0.02) *with harm for female sex*	1, 395 § (exact numbers in each group not mentioned)	Fazeli, 2014
MODS ≥6	Male vs female	Statistically significant: 21/64 vs 3/21 § aOR: 5.6, 95%CI [1.1; 27.8] (p<0.05) *with harm for male sex*	1, 64 vs 21	Cumming, 2001
		Not statistically significant: 104/143 vs 24/32 § aOR: 2.8, 95%CI [0.9; 8.4] (p>0.05)	1, 143 vs 32	Fitzwater, 2003
Severe sepsis/septic shock		Not statistically significant: 11/64 vs 1/21 § RR: 3.61, 95%CI [0.49; 26.32] (p=0.21)* ¥	1, 64 vs 21	Cumming, 2001
TSAB				

Mortality	20% vs 40% vs 100%	Statistically significant: 13/338 vs 60/93 vs 100/103 § (p<0.05) £† *with harm for greater area burned*	1, 338 vs 93 vs 103	Attia, 2000
Death risk (%)	% TBSA	Statistically significant: aOR: 1.24, 95%CI [1.15; 1.33] (p<0.0001) *With harm for greater area burned*	1, 395 § (exact numbers in each group not mentioned)	Fazeli, 2014
MODS ≥6	% TBSA	Statistically significant: aOR: 1.06, 95%CI [1.03; 1.10] (p<0.05) *with harm for greater area burned*	1, 24 § (no mention of different groups)	Cumming, 2001
Cause of burns				
Mortality	Flame vs non-flame	Not statistically significant: 164/356 vs 12/177 § (p>0.05) £†	1, 356 vs 177	Attia, 2000
Death risk (%)	Flame vs other causes	Not statistically significant: 35.7 vs 3.2 § aOR: 5.33, 95%CI [0.61; 1.29] (p=0.131)	1, 395 (exact numbers in each group not mentioned)	Fazeli, 2014
Amputation	Electrical vs other causes	Statistically significant: 33/214 vs 11/930 § (p<0.05) £† *with harm for electrical burns*	1, 310 vs 930	Tarim, 2013
Depth				
Mortality	Superficial vs deep	Statistically significant: 1/195 vs 175/337 § (p<0.05) £† *with harm for deep burns*	1, 195 vs 337	Attia, 2000
MODS ≥6	Full thickness burn ≥30%	Statistically significant: aOR: 7.6, 95%CI [3.2; 17.9] (p<0.05) *with harm for ≥30% TBSA burned*	1, 175 § (exact numbers in each group not mentioned)	Fitzwater, 2003
Degree				
Mortality	1st and 2nd vs 2nd vs 3rd vs 2nd and 3rd	Statistically significant: 1/28 vs 8/236 vs 1/7 vs 166/262 § (p<0.05)* £† *with harm for 2nd and 3rd degree wounds*	1, 28 vs 236 vs 7 vs 262	Attia, 2000
Inhalation injury				
Mortality	inhalation vs non-inhalation	Statistically significant: 7/7 vs 119/476 § (p<0.05) £† *with harm for inhalation*	1, 7 vs 357	Attia, 2000
MODS ≥6		Not statistically significant: 7/15 vs 17/70 § aOR: 1.7, 95%CI [0.41; 7.0] (p>0.05) ¥	1, 15 vs 70	Cumming, 2001

		Statistically significant: 34/46 vs 13/129 § aOR: 2.6, 95%CI [1.1; 6.9] ($p<0.05$) *With harm for inhalation*	1, 46 vs 129	Fitzwater, 2003

£ No effect size and CI available
¥ Imprecision (large variability of results)
† Imprecision (lack of data)
§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations
Attia, 2000	No	No	No, logistic regression analyses were performed	No	
Cumming, 2001	No	No	No, logistic regression analyses were performed	No	
Fazeli, 2014	No	No	No, multivariable logistic regression was performed	No, data on final outcome of 145 patients were missed, but these patients were not included in analysis	
Fitzwater	Yes, there was a significant difference in age in the severe MOD group	No	No, logistic regression was performed	No	
Tarim, 2013	Yes, there were significantly more males in the amputation group, and the mean age was significantly higher in the amputation group	No	No, multiple regression analyses were performed	No	

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes, lack of data and/or large variability of the results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Conclusion	**Age** There is limited evidence with harm for older age. It was shown that older age resulted in a statistically significant increased risk of mortality or severe multiple organ dysfunction, compared to younger age (Attia 2000, Cumming 2001). It was shown that being >60 years old resulted in a statistically significant increased risk of mortality, compared to being <15 years old (Fazeli 2014). It was shown that being ≥50 years old resulted in a statistically significant increased risk of severe multiple organ dysfunction, compared to younger age (Fitzwater 2003). A statistically significant increased risk of being 15-60 years old compared to being <15 years old on mortality, could not be demonstrated (Fazeli 2014). Evidence is of very low quality and results cannot be considered precise due to limited sample size, lack of data and/or large variability of results. **Sex** *Mortality* There is limited evidence with harm for female sex. It was shown that being female resulted in a statistically significant increased risk of mortality, compared to being male (Attia 2000, Fazeli 2014). Evidence is of very low quality and results cannot be considered precise due to limited sample size, lack of data and/or large variability of results. *Severe multiple organ dysfunction* There is limited evidence neither for the benefit/harm of being male nor being female. In making this conclusion, we placed a higher value on the larger study. A statistically significant increased risk of being male compared to being female on severe multiple organ dysfunction, could not be demonstrated (Fitzwater 2003). However, in another (smaller) study, it was shown that being male resulted in a statistically significant increased risk of severe multiple organ dysfunction, compared to being female (Cumming 2001). Evidence is of very low quality and results cannot be considered precise due to limited sample size, lack of data and/or large variability of results. **Total surface are burned (TSAB)** There is limited evidence with harm for total surface are burned. It was shown that a greater TSAB resulted in a statistically significant increased risk of mortality and severe multiple organ dysfunction, compared to a smaller TSAB (Attia 2000, Fazeli 2014, Cumming 2001). Evidence is of very low quality and results cannot be considered precise due to limited sample size, lack of data and/or large variability of results. **Cause of burns** There is limited evidence with harm for electrical burns. It was shown that electrical burns resulted in a statistically significant increased risk of amputation, compared to scald, flame, chemical or contact burns (Tarim 2013). Evidence is of very low quality and results cannot be considered precise due to limited sample size, lack of data and/or large variability of results. There is limited evidence neither for the benefit/harm of burn accidtens with flame nor other causes of burns. A statistically significant increased risk of mortality in case of burn accident with flames compared to other causes of burns, could not be demonstrated (Attia 2000, Fazeli 2014). Evidence is of very low quality and results of these studies are imprecise due to limited sample size, lack of data and/or large variability of results. **Depth of burns** There is limited evidence with harm for deep burns.

	It was shown that deep burns resulted in a statistically significant increased risk of mortality, compared to superficial burns (Attia 2000). Evidence is of very low quality and results cannot be considered precise due to limited sample size, lack of data and/or large variability of results. There is limited evidence with harm for full thickness burns ≥30%. It was shown that full thickness burns ≥30% resulted in a statistically significant increased risk of severe multiple organ dysfunction (Fitzwater 2013). Evidence is of very low quality and results cannot be considered precise due to limited sample size, lack of data and/or large variability of results. **Degree of burns** There is limited evidence with harm for 2nd and 3rd degree burns. It was shown that a combination of 2nd and 3rd degree burns resulted in a statistically significant increased risk of mortality, compared to 1st and 2nd combined, only 2nd or only 3rd degree burns (Attia 2000). Evidence is of very low quality and results cannot be considered precise due to limited sample size, lack of data and/or large variability of results. **Inhalation injury** There is limited evidence with harm for inhalation injury. In making this conclusion, we placed a higher value on the larger study. It was shown that inhalation burns resulted in a statistically significant increased risk of mortality and severe multiple organ dysfunction, compared to no inhalation burns (Attia 2000, Fitzwater 2013). However, in another smaller study, a statistically significant increased risk of inhalation injury compared to no inhalation injury on severe multiple organ dysfunction, could not be demonstrated (Cumming 2001). Evidence is of very low quality and results cannot be considered precise due to limited sample size, lack of data and/or large variability of results.
Reference(s)	**Articles** Attia AF, Reda AA, Mandil AM, Arafa MA, Massoud N. *Predictive models for mortality and length of hospital stay in an Egyptian burns centre*. Eastern Mediterranean Health Journal 2000, 6(5/6):1055-1061 Cumming J, Purdue GF, Hunt JL, O'Keefe GE. *Objective estimates of the incidence and consequences of multiple organ dysfunction and sepsis after burn trauma*. J Trauma 2001, 50:510-515 Fazeli S, Karami-Matin R, Kakaei N, Poutghorban S, Safari-Faramani R, Safari-Faramani B. *Predictive factors of mortality in burn patients*. Trauma Mon 2014, 19(1):e14480 Fitzwater J, Purdue GF, Hunt JL, O'Keefe GE. *The risk factors and time course of sepsis and organ dysfunction after burn trauma*. J Trauma 2003, 54:959-966 Tarim A, Ezer A. *Electrical burn is still a major risk factor for amputations*. Burns 2013, 39:354-357

Burns in respiratory tract – Drinking ice water (First Aid)

Question (PICO)	Among persons with burns in the respiratory tract (P), does drinking ice water (I) compared to not drinking ice water (C) change tissue healing, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Burns, inhalation"] 2. "burn*":ti,ab,kw AND (trachea:ti,ab,kw OR "inhalation":ti,ab,kw)

	3. 1-2 OR **MEDLINE** (via PubMed interface) using the following search strategy: 1. Burns, inhalation[Mesh] OR (burn*[TIAB] AND inhalation[TIAB]) 2. (Trachea[Mesh] OR Larynx[Mesh] OR Pharynx[Mesh] OR "respiratory tract"[TIAB] OR trachea[TIAB] OR larynx[TIAB] OR pharynx[TIAB]) 3. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'Lung burn'/exp OR (burn*:ab,ti AND inhalation:ab,ti) 2. trachea/exp OR larynx/exp OR pharynx/exp OR respiratory:ab,ti 3. 'wound healing'/exp OR ice:ab,ti OR water:ab,ti OR 'treatment':ab,ti OR 'therapy':ab,ti 4. 1-3 AND
Search date	17 February 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Snow blindness/arc-eye – Wet dressing (First Aid)

Question (PICO)	Among people with snow blindness or arc-eye (P), does applying wet dressings (I) compared to not applying wet dressings (C) change functional recovery, pain, complications, time to resumption of usual activity, restoration to pre-exposure condition, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "eye burns"] OR [mh "eye injuries"] OR [mh keratoconjunctivitis] OR (burn*:ti,ab,kw AND eye*:ti,ab,kw) OR keratoconjunctivitis:ti,ab,kw OR photokeratitis:ti,ab,kw 2. [mh Snow] OR [mh "snow sports"] OR [mh "ultraviolet rays"] OR ultraviolet:ti,ab,kw OR UV:ti,ab,kw OR [mh welding] OR weld*:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Eye burns"[Mesh] OR "eye injuries"[Mesh] OR keratoconjunctivitis[Mesh] OR (burn*[TIAB] AND eye*[TIAB]) OR keratoconjunctivitis[TIAB] OR photokeratitis[TIAB] 2. Snow[Mesh] OR "snow sports"[Mesh] OR "ultraviolet rays"[Mesh] OR ultraviolet[TIAB] OR UV[TIAB] OR welding[Mesh] OR weld*[TIAB] 3. 1 AND 2 4. snowblind*[TIAB] OR "arc-eye"[TIAB] 5. 3 OR 4 **Embase** (via Embase.com interface) using the following search strategy: 1. 'eye injury'/exp OR 'eye burn'/exp OR keratoconjunctivitis/exp OR (burn:ab,ti AND eye*:ab,ti) OR keratoconjunctivitis:ab,ti OR photokeratitis:ab,ti 2. Snow/exp OR 'winter sport'/exp OR 'ultraviolet radiation'/exp OR ultraviolet:ab,ti OR UV:ab,ti OR welding/exp OR weld*:ab,ti 3. 1 AND 2 4. snowblind*:ab,ti OR 'arc eye':ab,ti 5. 3 OR 4
Search date	05 June 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages with eye injury caused by UV-radiation in the snow or by welding. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available.

	An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Snow blindness/Arc-eye – Sunglasses/welding glasses (Prevention)

Question (PICO)	In humans (P), is wearing sunglasses or welding glasses (I) compared to not wearing sun- or welding glasses (C) effective to prevent snow blindness or arc eye (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "eye burns"] OR [mh "eye injuries"] OR [mh keratoconjunctivitis] OR (burn*:ti,ab,kw AND eye*:ti,ab,kw) OR keratoconjunctivitis:ti,ab,kw OR photokeratitis:ti,ab,kw 2. [mh Snow] OR [mh "snow sports"] OR [mh "ultraviolet rays"] OR ultraviolet:ti,ab,kw OR UV:ti,ab,kw OR [mh welding] OR weld*:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Eye burns"[Mesh] OR "eye injuries"[Mesh] OR keratoconjunctivitis[Mesh] OR (burn*[TIAB] AND eye*[TIAB]) OR keratoconjunctivitis[TIAB] OR photokeratitis[TIAB] 2. Snow[Mesh] OR "snow sports"[Mesh] OR "ultraviolet rays"[Mesh] OR ultraviolet[TIAB] OR UV[TIAB] OR welding[Mesh] OR weld*[TIAB] 3. 1 AND 2 4. snowblind*[TIAB] OR "arc-eye"[TIAB] 5. 3 OR 4 **Embase** (via Embase.com interface) using the following search strategy: 1. 'eye injury'/exp OR 'eye burn'/exp OR keratoconjunctivitis/exp OR (burn:ab,ti AND eye*:ab,ti) OR keratoconjunctivitis:ab,ti OR photokeratitis:ab,ti 2. Snow/exp OR 'winter sport'/exp OR 'ultraviolet radiation'/exp OR ultraviolet:ab,ti OR UV:ab,ti OR welding/exp OR weld*:ab,ti 3. 1 AND 2 4. snowblind*:ab,ti OR 'arc eye':ab,ti 5. 3 OR 4

	Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	05 June 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Chen, 2009, Taiwan	Observational: case-control study	283 work-related eye injury patients (mean age 40.2±13.1 years; 259 males, 24 females) were recruited in 2003-2006 from ophthalmic clinics and emergency departments in Taiwan.	wearing EPD vs not wearing EPD (eye protection device)	Case-crossover study: comparison of an individual's activity before the onset of the injury to the patient's usual activities
Ho, 2008, Taiwan	Observational: case-control study	31 cases (mean age 42.8±10.7 years; 26 males, 5 females) of work-related eye injuries during January 2003 to December 2004 at an ophthalmology ward in an academic medical center in Taiwan. 62 subjects who were enrolled in the Labor Insurance Program were selected as controls (41.8±10.5 years; 52 males, 10 females). Cases and controls were matched based on history of eye injury, gender, age and similar occupations.	wearing eye protection vs not wearing eye protection	

Yu, 2004, China	Observational: case-control study	239 patients (mean age 39.3 years±11.3 years; 220 males, 19 females) with work-related eye injuries attending the ophthalmology clinics of 3 major public hospitals in Hong Kong during first 3 months of 2000. Controls were selected from general population based on the residential telephone directory of Hong Kong. Controls (n=251) (mean age 38.2±12.5 years; 232 males, 19 females) were matched to cases based on gender.	wearing eye protection vs not wearing eye protection	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Eye injury	EPD vs no EPD	Statistically significant: OR: 0.4, 95%CI [0.2; 0.7], p<0.05 *In favour of EPD*	1, 283 § (within subjects)	Chen, 2009
	eye protection vs no eye protection	Statistically significant: 33/188 vs 37/103 OR: 0.36, 95%CI [0.20; 0.67], p=0.001* *In favour of eye protection*	2, 188 vs 103 §	Ho, 2008 and Yu, 2004

Mean ± SD (unless otherwise indicated)

* Calculations done by the reviewer(s) using Review Manager software

§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations
Chen, 2009	unclear, not specified in the article	yes, possible recall bias	unclear, not specified in the article	no	
Ho, 2008	No, cases and controls were matched based on history of eye injury, gender, age and similar occupations.	No	No, confounding factors were taken into account	No	hospital based design, possible self-selection bias
Yu, 2004	No, cases and controls were matched based on gender	No	No, different models were tested, taking into account several variables	No	hospital based design, possible self-selection bias

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/low number of events
Inconsistency	0	
Indirectness	-1	Study on eye injuries in general (photo keratitis is major cause of work-related eye injuries)
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Conclusion	There is limited evidence from 3 observational studies in favour of eye protection. It was shown that wearing eye protection resulted in a statistically significant decrease of work-related eye injuries, compared to not wearing eye protection (Chen 2009, Ho 2008, Yu 2004). Evidence is of very low quality and results cannot be considered precise due to limited sample size.
Reference(s)	**Articles** Chen S-Y, Fong P-C, Lin S-F, Chang C-H, Chan C-C. *A case-crossover study on transient risk factors of work-related eye injuries*. Occup Environ Med 2009, 66:517-522 Ho C-K, Yen Y-L, Chang C-H, Chiang H-C, Shen Y-Y, Chang P-Y. *Case-control Study on the Prevention of Occupational Eye Injuries*. Kaohsiung J Med Sci 2008, 24:10-6 Yu TSI, Liu HL, Hui K. *A Case-Control Study of Eye Injuries in the Workplace in Hong Kong*. Ophthalmology 2004, 111:70-74

Pepper spray – decontamination with tap water and other products (First Aid)

Question (PICO)	Among persons with eye exposure to pepper spray (P), does decontamination with tap water and other products (I) compared to tap water alone (C) change functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. "pepper spray":ti,ab,kw 2. "oleoresin capsicum":ti,ab,kw 3. "capsicum spray":ti,ab,kw 4. 1-3 OR **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Pepper spray"[TIAB] 2. "oleoresin capsicum"[TIAB] 3. "capsicum spray"[TIAB] 4. 1-3 OR **Embase** (via Embase.com interface) using the following search strategy: 1. 'Capsicum oleoresin'/exp 2. 'pepper spray':ab,ti 3. 'Oleoresin capsicum':ab,ti 4. 'capsicum spray':ab,ti 5. 1-4 OR

	Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	17 February 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Barry, 2008, USA	Experimental: randomized controlled trial	50 volunteers of military law enforcement trainees (44 men and 6 women), aged 18-36 years Subjects were randomized to 1 of 5 treatment groups	1. Antacid (Maalox – magnesium hydroxide-aluminium-hydroxide) 2. Lidocaine gel (2%) 3. Milk (grade A, pasteurized, homogenized, whole milk) 4. Baby shampoo (Johnson&Johnson, "no more tears" baby shampoo) 5. Tap water = control Exposure to pepper spray – 2 min situational training – self-decontamination with water – 1 of 5 treatments: cloths soaked in the substance, subjects were allowed to put cloth over face or use it as a wipe for painful areas.	Power calculation: 9 subjects per group (45 in total) were needed to detect a 2-SD or 1.0-cm difference

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Pain (visual analogue scale (VAS))	Decontamination with tap water and: 1. Antacid 2. Lidocaine 3. Milk 4. Baby shampoo 5. control	No statistically significant difference in pain between treatment groups (p>0.05) † (data shown in graph)	1, 49 (not mentioned in article how many in each group)	Barry, 2008

Mean ± SD (unless otherwise indicated)
† Imprecision (lack of data)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Barry, 2008	Unclear, not mentioned how randomization was done	No, participants were blinded, but could determine which treatment they were provided based on the properties	No	No	imprecision due to lack of data (although results are presented as a graph)

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	0	
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Moderate [B]**	

Conclusion	There is evidence from 1 experimental study, showing no difference between interventions and control: it was shown that tap water combined with antacid, lidocaine, milk of baby shampoo did not result in a statistically significant difference of pain, compared to tap water only (Barry 2008). Evidence is of moderate quality.
Reference(s)	**Articles** Barry JD, Hennessy R, McManus JG Jr. *A randomized controlled trial comparing treatment regimens for acute pain for topical Oleoresin Capsaicin (pepper spray) exposure in adult volunteers*. Prehosp Emerg Care 2008, 12(4):432-7

Pepper spray – Cleansing skin with a greasy product (First Aid)

Question (PICO)	Among persons with eye exposure to pepper spray (P), does cleansing with a greasy product (I) compared to not cleansing with a greasy product (C) change functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. "pepper spray":ti,ab,kw 2. "oleoresin capsicum":ti,ab,kw

	3. "capsicum spray":ti,ab,kw 4. 1-3 OR **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Pepper spray"[TIAB] 2. "oleoresin capsicum"[TIAB] 3. "capsicum spray"[TIAB] 4. 1-3 OR **Embase** (via Embase.com interface) using the following search strategy: 1. 'Capsicum oleoresin'/exp 2. 'pepper spray':ab,ti 3. 'Oleoresin capsicum':ab,ti 4. 'capsicum spray':ab,ti 5. 1-4 OR
Search date	16 June 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria
Reference(s)	/

Chemical burns – Irrigation with water (First Aid)

Question (PICO)	Among adults and children with chemical burns (P), does irrigation with water (I), compared with no irrigation (C), change pain, complications, wound healing, need for advanced medical care, patient satisfaction, rates of fasciotomy, depth or breadth of burn (Class 5) (O)?
Search Strategy	Databases **MEDLINE** (via PubMed interface) using the following search strategy: 1. "chemical burns"[Mesh] OR "chemical burn"[TIAB] OR "chemical burns"[TIAB] 2. First Aid Filter 3. 1-2 AND Articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	7 June 2014
In/Exclusion criteria	**Population**: Adults and children with chemical burns **Intervention**: irrigation with water **Comparison**: no irrigation or irrigation with other fluids such as saline. **Outcome**: Include: functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No evidence was found using the above mentioned search strategy and criteria
Reference(s)	/

Sunburn – Hydration (First Aid)

Question (PICO)	Among people with an acute sunburn (P) is hydrating the skin (I) compared to not hydrating the skin (C) effective to change tissue healing, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition and time to resolution of symptoms?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "sunburn"] OR sunburn*:ti,ab,kw OR sun:ti,ab,kw 2. [mh ointments] OR [mh emollients] OR ointment*:ti,ab,kw OR salve*:ti,ab,kw OR spray*:ti,ab,kw OR lotion*:ti,ab,kw OR aftersun:ti,ab,kw OR after-sun:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy (limits: humans): 1. "sunburn"[Mesh] OR sunburn*[TIAB] OR sun[TIAB] 2. "ointments"[Mesh] OR "emollients"[Mesh] OR ointment*[TIAB] OR salve*[TIAB] OR spray*[TIAB] OR lotion*[TIAB] OR aftersun[TIAB] OR after-sun[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy (limits: humans): 1. sunburn/exp OR sunburn*:ab,ti OR sun:ab,ti 2. ointment/exp OR 'emollient agent'/exp OR ointment*:ab,ti OR salve*:ab,ti OR spray*:ab,ti OR lotion*:ab,ti OR aftersun:ab,ti OR after-sun:ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	12 June 2015
In/Exclusion criteria	**Population:** Include: people with an acute sunburn. Exclude: people with erythema not caused by sunlight. **Intervention:** Include: emollients, sprays, creams, lotions, etc. that are commercially available and serve as a first aid intervention for an acute sunburn. Exclude: Interventions that do not take place during the acute phase which can be considered as aftercare. Interventions that are not commercially available and only can be used with a prescription form of a physician (e.g. products with corticosteroids) **Comparison:** Include: no intervention or placebo **Outcome**: Include: change tissue healing, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition and time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomized controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values.

	Language: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Hughes-Formella, 1998, Germany	Experimental: controlled interrupted time series (within-subjects design)	30 healthy volunteers (22 women, 11 men, mean age 36 years (range 19-64 years) were exposed to a UVB erythema test	Intervention 1: Hamamelis after sun lotion (pH5 Eucerin after sun lotion with 10% hamamelis distillate) Intervention 2: Hamamelis-free after sun lotion (pH5 Eucerin after sun lotion without hamamelis distillate) Control: no intervention (untreated) 300 microliter of each test preparation was applied occlusively to the treatment fields immediately following exposure of test fields to UVB and after measurement at 7 hours and 24 hours after irradiation.	Test field evaluation (chromametry and visual assessment) was performed at 7, 24 and 28 hours after irradiation. One hour before the measurement periods the occluding chambers were removed and test preparation residues removed with a soft disposable towel. The degree of erythema was visually assessed by a scale from 0 (no suppression of erythema) to 3 (complete suppression of erythema) Global differences were tested by repeated-measures ANOVA (and post-hoc Tukey tests)
Magnette, 2004, Switzerland	Experimental: randomized controlled trial	172 healthy volunteers (71 males and 101 females, mean age 32 years) suffering from an acute first-degree sunburn who received diclofenac-Na 0.1% Emulgel (intervention, n=114) or vehicle Emulgel (control, n=58)	Intervention: diclofenac-Na 0.1% Emulgel Control: Placebo (vehicle Emulgel) The substances (5 mg/cm^2) were applied twice after sun exposure (at 6 hours and at 10 hours)	
Puvabanditsin, 2005, Thailand	Experimental: controlled interrupted time series (within subjects design)	20 healthy volunteers (>18 years, no history of sun sensitivity or skin cancers in the family) exposed to artificial light (different dosages of Ultra-Violet type B, UVB: 40-80 milijoule)	Intervention: apply Aloe Vera cream immediately after UVB exposure Control: apply placebo 30 minutes prior and immediately after UVB exposure	The degree of erythema after UV exposure was scored from 0 (no erythema) to 4 (marked erythema) Pigmentation score was evaluated from 0

			The Aloe Vera cream/placebo was continuing applied twice daily for 3 weeks.	(no hyperpigmentation) to 4 (marked hyperpigmentation) Statistical analyses: p-values from non-parametric testing via Kruskal-Wallis one way analysis of variance by ranks among 4 groups (2 groups were not included in the context of this PICO question: Aloe Vera cream application before or before/after exposure)
Reuter, 2008, Germany	Experimental: Randomized controlled trial (within-subjects design)	40 healthy volunteers (19 males, 21 females – aged between 20 and 59 years) were exposed to a UVB erythema test	Intervention 1: Aloe Vera gel (97.5%) Intervention 2 (corticosteroid preparation): Dermallerg-Ratiopharm cream 1% (1% hydrocortisone) Intervention 3 (corticosteroid preparation): Dermatop cream (0.25% prednicarbate) Control 1: 1% hydrocortisone in placebo gel Control 2: a conventional gel base was used (water, glycerol 85%, phenoxyethanol, carbopol ETD 2020, sodium edetate, sodium hydroxide and perfume oil) Control 3: no intervention (untreated) The substances (20 mg per test area), were applied occlusively by tapes that were fixed with larger stripes of Fixomull. To prevent false measurements due to reactions to the tape, the	Erythema measurements were performed 3 times in each test site directly before the UV irradiation, 24 h after and after 48h after. Statistical analysis was performed by repeated-measures ANOVA

			tape was removed 23 h after substance application, i.e. 1 h before evaluation of the test areas. The same procedure was repeated a second time (day 2). [Only data from intervention 1 and control 2 and 3 were extracted (commercially-available products)]	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Degree of erythema (after 7 hours)	Hamamelis after sun vs untreated	Statistically significant: data represented in figure, only % reduction vs untreated reported in text: 20% reduction (p<0.05) £ *in favour of Hamamelis after sun*	1, 30 (within subjects) §	Hughes-Formella, 1998
	Hamamelis-free after sun lotion vs untreated	Statistically significant: data represented in figure, only % reduction vs untreated reported in text: 28% reduction (p<0.05) £ *in favour of Hamamelis-free after sun lotion*		
Degree of erythema (after 24 hours)	Aloe Vera cream vs placebo	Not statistically significant (for UVB dosages 40-80 mj): UVB 40 mj: 0.5 vs 0.75 (p=0.197) UVB 50 mj: 0.9 vs 1.05 (p=0.09) UVB 60 mj: 1.65 vs 2 (p=0.88) UVB 70 mj: 2.25 vs 2.1 (p=0.06) UVB 80 mj: 2.7 vs 2.95 (p=0.09) £	1, 20 (within subjects) §	Puvabanditsin, 2005
	Aloe Vera cream vs placebo/untreated	Not statistically significant: 29±52 vs 31±55 λ MD: -2 (p>0.05)	1, 40 (within subjects) §	Reuter, 2008
	Hamamelis after sun vs untreated	Statistically significant: data represented in figure, only % reduction vs untreated reported in text: 24% reduction (p<0.05) £ *in favour of Hamamelis after sun*	1, 30 (within subjects) §	Hughes-Formella, 1998
	Hamamelis-free after sun lotion vs untreated	Statistically significant: data represented in figure, only % reduction vs untreated reported in text: 11% reduction (p<0.05) £ *in favour of Hamamelis-free after sun*		
Degree of erythema (after 48 hours)	Aloe Vera cream vs untreated	Statistically significant: 18±39 vs 26±50 MD: -8 (p<0.05) λ *in favour of Aloe Vera cream*	1, 40 (within subjects) §	Reuter, 2008
	Aloe Vera cream vs placebo	Not statistically significant: 18±39 vs 18±41 MD: 0 (p>0.05) λ		
	Hamamelis after sun vs untreated	Statistically significant:	1, 30 (within subjects) §	Hughes-Formella, 1998

		data represented in figure, only % reduction vs untreated reported in text: 28% reduction (p<0.05) £ *in favour of hamamelis after sun*		
	Hamamelis-free after sun lotion vs untreated	Statistically significant: data represented in figure, only % reduction vs untreated reported in text: 16% reduction (p<0.05) £ *in favour of Hamamelis-free lotion*		
Spontaneous pain (mm.h) (after 7-54 hours)	diclofenac-Na 0.1% Emulgel vs placebo	Statistically significant: 370.1±455.6 vs 662±814.5 MD: -312.6, 95%CI [-478.9;-146.6] (p=0.0003) *in favour of diclofenac-Na 0.1% Emulgel*	1, 114 vs 58 §	Magnette, 2004
Provoked pain (mm.h) (after 7-54 hours)		Statistically significant: 384.3±471.3 vs 718±846.6 MD: -349.2, 95%CI [-520.1;-178.6] (p<0.0001) *in favour of diclofenac-Na 0.1% Emulgel*		
Erythema visual score (after 7-54 hours)		Statistically significant: 117.8±28.7 vs 138.1±33.6 MD: -21.1, 95%CI [-29.6;-12.6] (p<0.0001) *in favour of diclofenac-Na 0.1% Emulgel*		
Eryhtema colorimetry (after 7-54 hours)		Statistically significant: 350.8±111 vs 429.9±157.8 MD: -88.5, 95%CI [-114.2;-62.8] (p<0.0001) *in favour of diclofenac-Na 0.1% Emulgel*		
Total number of adverse events		Not statistically significant: 20/114 vs 11/58 RR: 0.93, 95%CI [0.48;1.8] (p=0.82)*		

Mean ± SD (unless otherwise indicated)

* Calculations done by the reviewer(s) using Review Manager software

§ Imprecision (limited sample size or low number of events)

λ Data extracted from graph

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Hughes-Formella, 1998	Yes, no randomisation	Yes	No	No	
Magnette, 2004	Unclear, not specified in the article	No	No	No	
Puvabanditsin, 2005	Unclear, not specified in the article	No	No	No	
Reuter, 2008	Unclear, not specified in the article	No	No	No	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Limited sample size
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Moderate [B]**	

Conclusion	There is limited evidence in favour of after sun lotion/gel/cream. In making this evidence conclusion, we place a higher value on outcomes measured at a longer term (48-54 hours after sun exposure) over outcomes measured at a shorter term (7-24 hours after sun exposure). It was shown that after sun lotion (Hamamelis(-free) lotion), after sun cream (Aloe Vera cream) or after sun gel (diclofenac-Na 0.1% Emulgel) resulted in a statistically significant reduced erythema and pain reduction (48-54 hours after sun exposure) compared to a placebo lotion/cream or no treatment (Hughes-Formella 1998, Magnette 2004, Reuter 2008). On the other hand, in 2 studies with aftersun cream (Aloe Vera cream) a statistical erythema reduction 24 hours after sun exposure, compared to placebo or no treatment, could not be demonstrated. (Puvabanditsin 2005, Reuter 2008). Evidence is of moderate quality and results cannot be considered precise due to limited sample size.
Reference(s)	**Articles** Hughes-Formella BJ, Bohnsack K, Rippke F, Benner G, Rudolph M, Tausch I, Gassmueller J. *Anti-inflammatory effect of hamamelis lotion in a UVB erythema test.* Dermatology 1998, 196:316-322. Magnette J, Kienzler JL, Alekxandrova I, Savaluny E, Khemis A, Amal S, Trabelsi M, Cesarini JP. *The efficacy and safety of low-dose diclofenac sodium 0.1% gel for the symptomatic relief of pain and erythema associated with superficial natural sunburn.* Eur J Dermatol 2004, 14:238-246. Puvabanditsin P, Vongtongsri R. *Efficacy of aloe vera cream in prevention and treatment of sunburn and suntan.* J Med Assoc Thai 2005, 88(SuppI4): S173-6. Reuter J, Jocher A, Stump J, Grossjohann B, Franke G, Schempp CM. *Investigation of the anti-inflammatory potential of Aloe vera gel (97.5%) in the ultraviolet erythema test.* Skin Pharmacol Physiol 2008, 21:106–110.

Sunburn – Sunscreen (Prevention)

Question (PICO)	In humans (P), is applying sunscreen (I) compared to not applying sunscreen (C) effective to prevent sunburn?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh Sunburn] OR sunburn*:ti,ab,kw OR [mh erythema] OR erythema*:ti,ab,kw 2. [mh "sunscreening agents"] OR sunscreen*:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Sunburn[Mesh] OR sunburn*[TIAB] 2. "Sunscreening agents"[Mesh] OR sunscreen*[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy:

	1. Sunburn/exp OR sunburn*:ab,ti 2. Sunscreen/exp OR sunscreen*:ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	17 June 2015
In/Exclusion criteria	**Population**: Include: healthy volunteers of all ages. **Intervention**: Include: use of sunscreen with different SPF factors. Exclude: studies on the combined use of sunscreen with other products. Methods of measuring SPF. **Outcome**: Include: sunburn, sunburn cells, sun protection factor (SPF), pain or other health outcome measures (including adverse effects). Exclude: behaviour change, observational studies on the use of sunscreen and prevalence of sunburns, measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Césarini, 1989, France	Experimental: non-randomized controlled trial (within subjects)	7 healthy Caucasian subjects (3 males, 4 females), aged between 20 and 45. Irradiation: bank of 4 Osram Ultravitalux medium-pressure mercury-arc lamps as recommended by DIN standard 67501. Irradiation was performed simultaneously on protected and unprotected test sites on the midback of the volunteers. 24h after irradiation, a 2 mm punch biopsy was performed to determine SBC.	Sunblock (Laboratories Galderma, Paris): 5 mg/cm^2 vs unprotected skin	SBC: sunburn cells MED: minimal erythema dose
Cole, 2014, USA	Experimental: non-randomized controlled trial	12 subjects (9 female, 3 male), age range 33-59 years, with Fitzpatrick skin type I-III. Their individual MED was measured prior to the treatments. 4 treatments were conducted on	1. Untreated control: no topical treatment with no UVR exposure 2. Positive control 1: no topical treatment	

		the lower back of each test subject	with 1 MED UVR exposure 3. Positive control 2: No topical treatment with 3 MEDs UVR exposure 4. Test treatment: topical SPF 55 treatment with 55 MEDs UVR exposure Sunscreen was applied at standard application dose of 2 mg/cm^2 and allowed to dry for minimum 15 minutes prior to UV exposure.	
Kaidbey, 1990, USA	Experimental: randomized controlled trial (within subjects)	16 healthy white adults between the ages of 18 and 54 years with sun-reactive skin types I, II or III. UV radiation (150-watt compact xenon arc solar simulator) exposures were given to normal-looking untanned areas of the skin on the middle of the back.	1. Sunscreen SPF 15 2. Sunscreen SPF 30 3. No sunscreen: unprotected adjoining area of normal skin Topical dose of sunscreen was 2 mg/cm^2.	
Odio, 1994, USA	Experimental: randomized controlled trial (within subjects)	98 healthy children, aged 7-12 years (57 males, 41 females) with Fitzpatrick skin types I, II and III. 49 children were randomly selected from this sample for inclusion in each of 2 separate studies. Study 1: 6h exposure interval during which participants received a total of 13 MED. Study 2: 8h test period with a total exposure of 21 MED. For both studies, baseline dermatological evaluations were obtained for each child.	1. Single sunscreen application 2. Multiple sunscreen applications Parents or guardians were instructed to apply test sunscreen, liberally and evenly to all exposed body areas of their child followed by a 15 min waiting period. Child was given free access to beach. Activity cycle: 60 min unrestricted activity – 15 min required swimming + towel drying – 20 in the shade for evaluation and product reapplication (to single lateral half of body)	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Sunburn cells	Protected vs unprotected skin	Not statistically significant: 2.0±1.3 vs 3.7±7.5 MD: -1.7 £† (p>0.05)	1, 7 § (within subjects)	Césarini, 1987
	Sunscreen treated 55 MED radiation vs untreated 1 MED radiation	Not Statistically significant: 1.91±2.39 vs 2.92±4.50 MD: -1.01 £†	1, 11 § (within subjects)	Cole, 2014

		(p>0.05)		
	Sunscreen treated 55 MED radiation vs untreated 3 MED radiation	Statistically significant: 1.91±2.39 vs 18.00±10.04 MD: -16.09 £ (p<0.05) *In favour of sunscreen treated*		
	Sunscreen SPF 15 vs no sunscreen	Statistically significant: 7.45±8.12 vs 19.57±26.75 MD: -12,12 £ (p<0.05) *In favour of sunscreen SPF 15*	1, 16 § (within subjects)	Kaidbey, 1990
	Sunscreen SPF 30 vs no sunscreen	Statistically significant: 2.96±4.40 vs 19.57±26.75 MD: -16.61 £ (p<0.05) *In favour of sunscreen SPF 30*		
	Sunscreen SPF 15 vs sunscreen SPF 30	Statistically significant: 7.45±8.12 vs 2.96±4.40 MD: -12,12 £ (p<0.05) *In favour of sunscreen SPF 30*		
Erythema grade after exposure to 21 MED	one vs five applications	erythema grade 0: Statistically significant: 25/49 vs 41/49 § OR: 0.2 £ (p<0.01) *In favour of five applications* erythema grade 1: Statistically significant: 14/49 vs 7/49 § OR: 2.4 £ (p<0.01) *In favour of five applications* erythema grade 2: Statistically significant: 8/49 vs 0/49 § OR: 20.28 £ (p<0.01) *In favour of five applications*	1, 49 (within subjects)	Odio, 1994

Mean ± SD (unless otherwise indicated)
£ No CI available
§ Imprecision (limited sample size or low number of events)
† Imprecision (lack of data)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Césarini, 1989	yes, non-randomized within subjects	yes	yes, 12 subjects enrolled, only data of 11 subjects available	no	
Cole, 2014	unclear, not mentioned	yes	no	no	
Kaidbey, 1990	unclear, not mentioned	yes	no	no	
Odio, 1994	unclear, not mentioned	yes	no	no	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/lack of data
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is limited evidence from 4 experimental studies in favour of sunscreen. It was shown that sunscreen resulted in a statistically significant decrease of sunburn cells, compared to no sunscreen (Cole 2014, Kaidbey 1990). Furthermore it was shown that a higher SPF sunscreen resulted in a statistically significant decrease of sunburn cells, compared to a lower SPF sunscreen (Kaidbey 1990). However, in one study a statistically significant decrease of sunburn cells in protected versus unprotected skin could not be demonstrated (Césarini 1987). There is limited evidence from 1 study in favour of multiple applications of sunscreen. It was shown that five applications of sunscreen resulted in a statistically significant decrease of erythema, compared to one application of sunscreen (Odio 1994) Evidence is of low quality and results cannot be considered precise due to limited sample size and/or lack of data.
Reference(s)	**Articles** Césarini JP, Chardon A, Binet O, Hourseau C, Grollier JF. *High-protection sunscreen formulation prevents UVB-induced sunburn cell formation*. Photodermatology 1989, 6:20-23 Cole C, Appa Y, Ou-Yang H. *A broad spectrum high-SPF photostable sunscreen with a high UVA-PF can protect against cellular damage at high UV exposure doses*. Photodermatol Photoimmunol Photomed 2014, 30:212-219 Kaidbey KH. *The photoprotective potential of the new superpotent sunscreens*. J Am Acad Dermatol 1990, 22:449-52 Odio MR, Veres DA, Goodman JJ, Irwin C, Robinson LR, Martinez J, Kraus AL. *Comparative efficacy of sunscreen reapplication regimens in children exposed to ambient sunlight*. Photodermatol Photoimmunol Photomed 1994, 10:118-125

Sunburn – Sunscreen + insect repellent (Prevention)

Question (PICO)	In humans (P), is the combined used of sunscreen and insect repellent (I) compared to only using sunscreen (C) effective to prevent sunburn (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh Sunburn] OR sunburn*:ti,ab,kw OR [mh erythema] OR erythema*:ti,ab,kw 2. [mh "sunscreening agents"] OR sunscreen*:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Sunburn[Mesh] OR sunburn*[TIAB] 2. "Sunscreening agents"[Mesh] OR sunscreen*[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Sunburn/exp OR sunburn*:ab,ti 2. Sunscreen/exp OR sunscreen*:ab,ti

	3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	17 June 2015
In/Exclusion criteria	**Population**: Include: healthy volunteers of all ages. **Intervention**: Include: combined use of sunscreen and insect repellents. Exclude: studies on the use of sunscreen or insect repellent alone. **Outcome**: Include: sunburn, sunburn cells, sun protection factor (SPF), pain or other health outcome measures (including adverse effects). Exclude: behaviour change, measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Montemarano, 1997, USA	Experimental: Randomized controlled trial	14 volunteers assigned to one of 7 regimens (2 volunteers in each group)	1. Sunscreen alone with SPF after 15 min 2. Sunscreen with insect repellent after 15 min 3. Sunscreen with insect repellent after 45 min 4. Sunscreen with insect repellent after 75 min 5. Sunscreen with insect repellent after 105 min 6. Sunscreen alone with SPF after 105 min 7. Insect repellent alone with SPF after 15 min Sunscreen: Coppertone Sport SPF 15 Insect repellent: polymer formulation containing 33% diethylmethylbenzamide (DEET)	SPF = minimum amount of UVR necessary to produce erythema in a 1 cm^2 area of skin protected with 2 µl sunscreen divided by the amount of UVR necessary to produce erythema in unprotected skin. Sun protection factor (SPF) was measured 15 minutes after application of last substance

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
SPF	sunscreen with insect repellent (after 15-75 min) vs sunscreen alone with SPF after 15 min	Statistically significant: 12.45 vs 18.7 MD: 6.25 Mean decrease of 33.5% p<0.001†£ *In favour of sunscreen alone*	1, 8 vs 2 §	Montemarano, 1997
	sunscreen with insect repellent (after 105 min) vs sunscreen alone with SPF after 105 min	13.5 vs 18.8 †£ MD: 5.3 Mean decrease of 28% no p-value available	1, 2 vs 2 §	

Outcome measures expressed as Means
* Calculations done by the reviewer(s) using Review Manager software
£ No raw data/SD's available, effect size and CI cannot be calculated
† Imprecision (lack of data)
§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Montemarano, 1997	Unclear, not mentioned	Unclear, not mentioned	No	No	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/lack of data
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is limited evidence from 1 experimental study in favour of sunscreen alone. It was shown that sunscreen combined with insect repellent resulted in a statistically significant decrease of sun protection factor, compared to sunscreen alone (Montemarano 1997). Evidence is of low quality and results cannot be considered precise due to limited sample size and lack of data.
Reference(s)	**Articles** Montemarano AD, Gupta RK, Burge JR, Klein K. *Insect repellents and the efficacy of sunscreens*. Lancet 1997, 349:1670-1671

Sunburns – Aloe Vera (Prevention)

Question (PICO)	In humans (P), is the use of Aloe Vera (I) compared to not using Aloe Vera (C) effective to prevent sunburn?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh Sunburn] OR sunburn*:ti,ab,kw OR [mh erythema] OR erythema*:ti,ab,kw 2. [mh aloe] OR "aloe vera":ti,ab,kw 3. 1-2 AND

	MEDLINE (via PubMed interface) for experimental and observational studies using the following search strategy (limits: humans): 1. Sunburn[Mesh] OR sunburn*[TIAB] OR erythema[Mesh] OR erythema*[TIAB] 2. Aloe[Mesh] OR "aloe vera"[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy (limits: humans): 1. Sunburn/exp OR sunburn*:ab,ti OR erythema/exp OR erythema*:ab,ti 2. 'aloe vera'/exp OR 'aloe vera':ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	16 June 2015
In/Exclusion criteria	**Population:** Include healthy volunteers of all ages. Exclude: people with sunburn or erythema caused by sunlight. **Intervention:** Include: emollients, sprays, creams, lotions, etc. with Aloe Vera that are commercially available and serve as an intervention for the prevention of acute sunburn. Exclude: Interventions that do not take place during the acute phase which can be considered as aftercare. Interventions that are not commercially available and only can be used with a prescription form of a physician (e.g. products with corticosteroids) **Comparison:** Include: no intervention or placebo **Outcome**: Include: change tissue healing, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition and time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomized controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Puvabanditsin, 2005, Thailand	Experimental: controlled interrupted time series (within subjects design)	20 healthy volunteers (>18 years, no history of sun sensitivity or skin cancers in the family) exposed to artificial light (different dosages of Ultra-Violet type	1. apply Aloe Vera cream 30 min prior to UVB exposure 2. Aloe Vera cream immediately after UVB exposure 3. Aloe Vera cream 30 min prior and immediately after UVB exposure	The degree of erythema after UV exposure was scored from 0 (no erythema) to 4 (marked erythema) Pigmentation score was evaluated from 0 (no hyperpigmentation) to 4

		B, UVB: 40-80 milijoule)	4. apply placebo 30 minutes prior and immediately after UVB exposure The Aloe Vera cream/placebo was continuing applied twice daily for 3 weeks.	(marked hyperpigmentation) Statistical analyses: p-values from non-parametric testing via Kruskal-Wallis one way analysis of variance by ranks among 4 groups (2 groups were not included in the context of this PICO question: Aloe Vera cream application before or before/after exposure)

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Degree of erythema (after 24 hours)	Aloe Vera cream vs placebo	Not statistically significant: UVB 40 mj: 0.35 vs 0.75 (p=0.197) UVB 50 mj: 0.55 vs 1.05 (p=0.09) UVB 60 mj: 1.3 vs 2 (p=0.88) UVB 70 mj: 1.85 vs 2.1 (p=0.06) UVB 80 mj: 2.5 vs 2.95 (p=0.09) £†	1, 20 (within-subjects) §	Puvabanditsin, 2005

Mean ± SD (unless otherwise indicated)
* Calculations done by the reviewer(s) using Review Manager software
§ Imprecision (limited sample size or low number of events)
£ No SD's available, effect size and CI cannot be calculated
† Imprecision (lack of data)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Puvabanditsin, 2005	Unclear, not specified in the article	No	No	No	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Limited sample size
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Moderate [B]**	

Conclusion	There is limited evidence from 1 experimental study, neither in favour of the intervention nor the control. A statistically significant decrease of sunburn, using aloe vera cream compared to placebo cream, could not be demonstrated (Puvabanditsin 2005). Evidence is of moderate quality and results of this study are imprecise due to limited sample size and lack of data.
Reference(s)	**Articles** Puvabanditsin P, Vongtongsri R. *Efficacy of aloe vera cream in prevention and treatment of sunburn and suntan.* J Med Assoc Thai 2005, 88(SuppI4): S173-6.

Sunburn – Sunless tanning (Prevention)

Question (PICO)	In humans (P), is the use of sunless tanning (I) compared to not using sunless tanning (C) effective to prevent sunburn?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: "sunless tanning":ti,ab,kw OR dihydroxyacetone:ti,ab,kw OR "self-tanner*":ti,ab,kw **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Sunburn[Mesh] OR sunburn*[TIAB] OR erythema[Mesh] OR erythema*[TIAB] 2. "Sunless tanning"[TIAB] OR "dihydroxyacetone"[TIAB] OR "self-tanner*"[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Sunburn/exp OR sunburn*:ab,ti OR erythema/exp OR erythema*:ab,ti 2. 'sunless tanning':ab,ti OR 'dihydroxyacetone':ab,ti OR 'self-tanner':ab,ti OR "self-tanners":ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	15 June 2015
In/Exclusion criteria	**Population**: Include: Healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included (but considered as indirect evidence). In case of preventive interventions: studies on primary prevention of sunburn at household or community levels that describe interventions with a potential immediate effect. Studies on preventive programmes or campaigns that consist of training or provision of an information leaflet, booklet, sticker. Use of dihydroxyacetone cream. Exclude: Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. Secondary or tertiary prevention. Interventions at policy level. Interventions based on drugs or vaccines. The following programmes: one-to-one programmes, home safety checks, free provision of materials, peer tutoring, information from medical doctors. Studies specifically intended for industrially specific situations (workplace related). Exposure to sun or solarium during past 2 months and numerous freckles and nevi. **Outcome**: Include: health outcome measures (including adverse effects). Studies on the incidence of accidents. Exclude: studies on feasibility of or compliance with interventions (behavioural outcomes). Measures of knowledge or attitudes. Self-reported outcomes. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies. **Language**: Include: English **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Faurschou, 2004, Denmark	Experimental: randomized controlled trial (within subjects)	20 healthy volunteers (20-45 years) Skin was treated with DHA and 22 – 26 hours after last application, a phototest was performed with simulated sunlight. Minimal erythema dose (MED) was determined 22-26 hours after UV exposure. Sun Protection Factor (SPF) was determined.	Dihydroxyacetone (DHA)-treated skin vs nontreated skin Four 40 cm^2 areas on the upper back of each participant were treated with 5% or 20% DHA cream once or three times. Four areas on the volar aspect of the forearms were treated in the same way as the back.	SPF = (dose to MED on DHA-treated skin) / (dose to MED to nontreated skin)

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
SPF (median (range))	5% DHA vs no treatment	1 application: Statistically significant: 1.3 (1.0-2.0) (p<0.001)†£ *In favour of 5% DHA* 3 applications: Statistically significant: 1.6 (1.3-2.4) (p<0.001)†£ *In favour of 5% DHA*	1, 20 § (within subjects)	Faurschou, 2004
	20% DHA vs no treatment	1 application: Statistically significant: 1.6 (1.0-2.0) (p<0.001)†£ *In favour of 20% DHA* 3 applications: Statistically significant: 2.2 (1.6-3.0) (p<0.001)†£ *In favour of 20% DHA*		

Mean ± SD (unless otherwise indicated)
* Calculations done by the reviewer(s) using Review Manager software
£ No raw data/SD's available, effect size and CI cannot be calculated
§ Imprecision (limited sample size or low number of events)
† Imprecision (lack of data)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Faurschou, 2004	No, areas were randomized and concealment was irrelevant (within subjects)	No	No	No	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes, lack of data
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Moderate [B]**	

Conclusion	There is limited evidence from 1 experimental study. It was shown that sunless tanning resulted in a statistically significant increase of sun protection factor, compared to no treatment (Faurschou 2004). Evidence is of moderate quality and results cannot be considered precise due to limited sample size and lack of data.
Reference(s)	**Articles** Faurschou A, Janjua NR, Wulf HC. *Sun protection effect of dihydroxyacetone*. Arch Dermatol 2004, 140:886-7

Sunburn – Polypodium leucotomos (Prevention)

Question (PICO)	In humans (P), is the use of *Polypodium leucotomos* (I) compared to not using *Polypodium leucotomos* (C) effective to prevent sunburn?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh Sunburn] OR sunburn*:ti,ab,kw OR [mh erythema] OR erythema*:ti,ab,kw 2. [mh Polypodium] OR "polypodium leucotomos":ti,ab,kw OR fern*:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Sunburn[Mesh] OR sunburn*[TIAB] OR erythema[Mesh] OR erythema*[TIAB] 2. Polypodium[Mesh] OR "polypodium leucotomos"[TIAB] OR fern*[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Sunburn/exp OR sunburn*:ab,ti OR erythema/exp OR erythema*:ab,ti 2. Polypodium/exp OR 'polypodium leucotomos extract'/exp OR 'polypodium leucotomos':ab,ti OR fern*:ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	12 June 2015

In/Exclusion criteria	**Population**: Include: Healthy volunteers of all ages. **Intervention**: Include: Studies including topical or oral *Polypodium leucotomos*. **Comparison:** topical oral or topical PL compared control (no treatment), placebo or sunscreen **Outcome**: Include: health outcome measures (including adverse effects). Studies on the incidence of accidents. Exclude: studies on feasibility of or compliance with interventions (behavioral outcomes). Measures of knowledge or attitudes. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies. **Language**: Include: English **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Gonzalez, 1997, USA	Experimental: Non-randomised controlled trial	21 paid volunteer subjects with skin phototype III and IV. Subjects were randomly divided into 2 major groups: non-photosensitzed (n=13) or photosensitized with psoralen (n=8) [data of photosensitized subjects were not extracted] Test subjects were asked to lie down in prone position in the sun and several adhesive patches, each with at least 6 precut 2x2 cm size exposure windows were affixed to the back. The study was carried out in Spain.	1. Control (n=13) 2. Standard sunscreen: SPF15 (n=5) 3. Topical PL (10%, 25%, 50%) 4. Oral PL (n=8): each subject received 240 mg PL 3x on one day prior to sun exposure and an additional dose of 360 mg PL 3h before sun exposure (=total oral dose of 1080 mg/subject)	PL=*Polypodium leucotomos* All subjects were their own control. Standard sunscreen and topical PL were applied to the same 5 subjects, oral PL was taken by 8 other subjects. Data for 25% and 50% topical PL are not shown, since they gave complete protection at all exposure sites of graded exposure doses in all test subjects.
Middelkamp-Hup, 2004, USA	Experimental: Non-randomised controlled trial (within subjects)	9 healthy participants (25-46 years; 5 men, 4 women) with skin phenotype II or III. The back of the skin was used. A solar simulator consisting of a 1000-W high pressure xenon arc-lamp was used as radiation source (305-400 nm)	MED was assessed of each participant. 1. Control: 6 or 7 skin sites were exposed to UVR without PL (MED, 2x MED or 3x MED) 2. PL (7.5 mg/kg body weight): first dose of oral PL the evening before second exposure. Next day second dose of oral PL, followed by exposure (same set	MED = minimal erythema dose = minimal dose of UVR inducing confluent erythema at 20-24 hours with 4 sharp borders of the exposed skin site.

			of exposures as in control) at different time points: 30 min, 1 hr, 1.5 hrs, 2 hrs and 3 hrs of ingestion of oral PL)	
Nestor, 2015, USA	Experimental: randomized controlled trial	40 healthy adults (18-65 years) with Fitzpatrick skin types I t IV. Subjects were randomized to receive *P. leucotomos* extract (n=20) or placebo (n=20)	1. PL group: capsules of 240 mg *P. leucotomos* extract (Heliocare® capsules). 2. Placebo group: inert capsule of similar appearance Subjects received 240 mg of *P. leucotomos* extract or placebo twice daily at approximately 8AM and 2PM for two months.	A sample of 40 subjects randomly assigned to two treatment groups was determined to be sufficient to achieve the safety endpoints.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Topical *Polypodium leucotomos* (PL)				
Immediate pigment darkening reaction (min)	10% topical PL vs control	Statistically significant: 56.0±16.73 vs 25.9±10.62 MD: 29.10 £ (p<0.01) *In favour of 10% topical PL*	1, 5 vs 8 § (within subjects)	Gonzalez, 1997
	10% topical PL vs Sunscreen	Statistically significant: 56.0±16.73 vs 80.0±14.14 MD: -24.00 £ (p<0.05) *In favour of sunscreen*	1, 5 vs 5 § (within subjects)	
Minimal Erythema Dose	10% topical PL vs control	Statistically significant: 80.0±0.0 vs 34.0±5.47 MD: 46.0 £ (p<0.001) *In favour of 10% topical PL*	1, 5 vs 8 § (within subjects)	
Oral *Polypodium leucotomos* (PL)				
Immediate pigment darkening reaction (min)	Oral PL vs control	Statistically significant: 75.0±17.32 vs 25.9±10.62 MD: 49.10, 95%CI [35.02; 63.18 (p<0.00001)* *In favour of oral PL*	1, 8 vs 8 §	Gonzalez, 1997
	Oral PL vs Sunscreen	Not statistically significant: 75.0±17.32 vs 80.0±14.14 MD: -5.00, 95%CI [-22.25; 12.25] (p=0.57)*	1, 8 vs 5 §	
MED	Oral PL vs control	Statistically significant: 98.0±15.35 vs 34.0±5.47 MD: 64.0, 95%CI [52.71; 75.29] (p<0.00001)* *In favour of oral PL*	1, 8 vs 8 §	

Sunburn cells/mm epidermis (at 24 hrs)	Oral PL vs control	Statistically significant: 16.3±2.9 vs 22.4±2.03 MD: -6.10, 95%CI [-8.41; -3.79] (p<0.00001) *In favour of oral PL*	1, 9 vs 9 § (within subjects)	Middelkamp-Hup, 2004
≥1 sunburn	Oral PL vs placebo	Statistically significant: 2/20 vs 8/20 OR: 0.17, 95%CI [0.03; 0.92] (p=0.04)* *In favour of oral PL*	1, 20 vs 20	Nestor, 2015
Change in MED		Statistically significant: 8/20 vs 1/20 OR: 12.67, 95%CI [1.40, 114.42] (p=0.02)* *In favour of oral PL*		
Change in UV-induced erythema intensity		Statistically significant: 10/20 vs 3/20 OR: 5.67, 95%CI, [1.25, 25.61] (p=0.02)* *In favour of oral PL*		

Mean ± SD (unless otherwise indicated)
£ No CI available
* Calculations done by the reviewer(s) using Review Manager software
§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Gonzalez, 1997	Yes, but irrelevant (within subjects)	Yes, but irrelevant (within subjects)	No	No	Study was partially funded by Industrial Farmaceutica Cantabria (the company that provided the PL capsules)
Middelkamp-Hup, 2004	Yes, but irrelevant (within subjects)	Yes, but irrelevant (within subjects)	No	No	Study of funded by a research grant from Industrial Farmaceutica Cantabria (the company that provided the PL capsules).
Nestor, 2015	Unclear, not mentioned	No, use of placebo	No	No	Study of funded by Ferndale Healthcare (the company that provided the PL capsules). Two of the three authors are consultants for and receive research grants from Ferndale Healthcare

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes
Inconsistency	0	
Indirectness	0	
Publication bias	-1	See table 'Quality of evidence'
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	**Topical *Polypodium leucotomos* (PL)** There is limited evidence from 1 experimental studies in favour of topical *Polypodium leucotomos*. It was shown that topical *Polypodium leucotomos* resulted in a statistically significant increase of time to immediate pigmentation darkening and minimal erythema dose, compared to no treatment (Gonzalez, 1997). However, it was shown that topical *Polypodium leucotomos* resulted in a statistically significant decrease of time to immediate pigmentation darkening, compared to sunscreen (Gonzalez, 1997). Evidence is of low quality and results cannot be considered precise due to limited sample size. **Oral *Polypodium leucotomos* (PL)** There is limited evidence from 3 experimental studies in favour of oral *Polypodium leucotomos*. It was shown that oral *Polypodium leucotomos* resulted in a statistically significant increase of time to immediate pigmentation darkening and minimal erythema dose, compared to no treatment or placebo (Gonzalez 1997, Nestor 2015). Furthermore, it was shown that oral *Polypodium leucotomos* resulted in a statistically significant decrease of sunburn cells/mm epidermis and UV-induced erythema intensity, compared to no treatment or placebo (Middelkamp-Hup 2004, Nestor 2015). A statistically significant increase of time to immediate pigmentation darkening, using oral PL compared to sunscreen, could not be demonstrated (Gonzalez 2004). Evidence is of low quality and results cannot be considered precise due to limited sample size.
Reference(s)	**Articles** González S, Pathak MA, Cuevas J, Villarrubia VG, Fitzpatrick TB. *Topical or oral administration with an extract of* Polypodium leucotomos *prevents acute sunburn and psoralen-induced phototoxic reactions as well as depletion of Langerhans cells in human skin*. Photodermatol Photoimmunol Photomed 1997, 13:50-60 Middelkamp-Hup MA, Pathak MA, Parrado C, Goukassian D, Rius-Díaz F, Mihm MC, Fitzpatrick TB, González S. *Oral* Polypodium leucotomos *extract decreases ultraviolet-induced damage of human skin*. J Am Acad Dermatol 2004, 51:910-8 Nestor MS, Berman B, Swenson N. *Safety and efficacy of oral* Polypodium leucotomos *extract in healthy adult subjects*. J Clin Aesthet Dermatol 2015: 8(2):19-23

Sunburn – Sunbed (Prevention)

Question (PICO)	In humans (P), is the use of a sunbed (I) compared to not using a sunbed (C) effective for laypeople to prevent sunburn (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: Sunbed*:ti,ab,kw OR sunlamp:ti,ab,kw OR "tanning booth":ti,ab,kw OR solari*:ti,ab,kw OR ((commercial:ti,ab,kw OR cosmetic:ti,ab,kw) AND tanning:ti,ab,kw) **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Sunburn[Mesh] OR sunburn*[TIAB] 2. Sunbed*[TIAB] OR sunlamp[TIAB] OR "tanning booth"[TIAB] OR solari*[TIAB] OR ((commercial[TIAB] OR cosmetic[TIAB]) AND tanning[TIAB]) 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Sunburn/exp OR sunburn*:ab,ti 2. Sunbed*:ab,ti OR sunlamp:ab,ti OR "tanning booth":ab,ti OR solari*:ab,ti OR ((commercial:ab,ti OR cosmetic:ab,ti) AND tanning:ab,ti) 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	11 June 2015
In/Exclusion criteria	**Population:** Include: sick or injured people or healthy volunteers of all ages. **Intervention:** Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included (but considered as indirect evidence). In case of preventive interventions: studies on primary prevention of injuries and diseases at household or community levels that describe interventions with a potential immediate effect. Studies on preventive programmes or campaigns that consist of training or provision of an information leaflet, booklet, sticker. Exclude: Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. Secondary or tertiary prevention. Interventions at policy level. Interventions based on drugs or vaccines. The following programmes: one-to-one programmes, home safety checks, free provision of materials, peer tutoring, information from medical doctors. Studies specifically intended for industrially specific situations (workplace related) **Outcome**: Include: health outcome measures (including adverse effects). Studies on the incidence of accidents. Exclude: studies on feasibility of or compliance with interventions (behavioural outcomes). Measures of knowledge or attitudes. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies. **Language**: Include: English

	Publication year: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria
Reference(s)	/

HEAD AND NECK

Syncope – Cold on forehead (First Aid)

Question (PICO)	In humans with a syncope (P), is a cold or humid compress on the forehead (I) compared to no cold on the forehead (C) effective to change functional recovery, complications, time to resumption of usual activities, restoration to the pre-exposure condition, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Syncope"] OR syncope:ti,ab OR fainting:ti,ab 2. [mh "Cryotherapy"] OR [mh "Ice"] OR [mh "Cold Temperature"] OR ice:ti,ab OR cryotherapy:ti,ab OR cold:ti,ab 3. 1 AND 2 **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Syncope"[Mesh] OR syncope[TIAB] OR fainting[TIAB] OR faintness[TIAB] 2. "Cryotherapy"[Mesh] OR "Ice"[Mesh] OR "Cold Temperature"[Mesh] OR Ice[TIAB] OR cryotherapy[TIAB] OR cold[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'faintness'/exp OR syncope:ab,ti OR fainting:ab,ti OR faintness:ab,ti 2. cryotherapy/exp OR Ice/exp OR 'cold'/exp OR ice:ab,ti OR cryotherapy:ab,ti OR cold:ab,ti 3. 1-2 AND
Search date	10 August 2015
In/Exclusion criteria	**Population**: Include: people with syncope **Intervention**: Include: use of ice, cold pack, ice pack, cold compress on the forehead **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion(s)	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Syncope – Leg raising (First Aid)

Question (PICO)	In an individual with a syncope (P), is leg raising (I) compared to no leg raising (C) effective to change functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Syncope"] OR syncope:ti,ab OR fainting:ti,ab OR faintness:ti,ab OR [mh hypotension] OR hypotension:ti,ab 2. [mh "Posture"] OR posture:ti,ab OR trendelenburg:ti,ab 3. 1 AND 2 **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Syncope"[Mesh] OR syncope[TIAB] OR fainting[TIAB] OR faintness[TIAB] OR "Hypotension"[Mesh] OR hypotension[TIAB] 2. (leg[TIAB] OR legs[TIAB]) AND rais*[TIAB] 3. "Head-Down Tilt"[Mesh] OR trendelenburg[TIAB] OR "lie down"[TIAB] OR "lying down" [TIAB] 4. 2 OR 3 5. 1 AND 4 **Embase** (via Embase.com interface) using the following search strategy: 1. 'faintness'/exp OR syncope:ab,ti OR fainting:ab,ti OR faintness:ab,ti OR 'hypotension'/exp OR hypotension:ab,ti 2. (leg:ab,ti OR legs:ab,ti) AND rais*:ab,ti 3. trendelenburg:ab,ti OR 'lie down':ab,ti OR 'lying down':ab,ti 4. 2 OR 3 5. 1 AND 4
Search date	10 August 2015
In/Exclusion criteria	**Population**: Include: people with syncope, healthy people with induced syncope, people with hypotension; Exclude: patients with autonomic failure, neurogenic orthostatic hypotension, idiopathic orthostatic hypotension, critically ill patients, cardiac patients **Intervention**: Include: (passive) leg raising, Trendelenburg position **Comparison**: Include: no specific posture, lying down **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available.

	An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion(s)	No relevant studies were identified using the above search strategy and criteria (people with syncope or hypotension, or healthy people with induced syncope).
Reference(s)	/

Syncope – Drinking (Prevention)

Question (PICO)	In humans (P), is drinking (I) compared to no intervention (C) effective to prevent syncope (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Syncope"] OR syncope:ti,ab OR fainting:ti,ab OR faintness:ti,ab OR "tilt-table test" 2. [mh "drinking"] OR [mh "water"] OR drinking:ti,ab OR water:ti,ab 3. 1 AND 2 **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Syncope"[Mesh] OR syncope[TIAB] OR fainting[TIAB] OR faintness[TIAB] OR "Tilt-Table Test"[Mesh] 2. "Drinking"[Mesh] OR "Water"[Mesh] OR drinking[TIAB] OR water[TIAB] 3. 1 AND 2 **Embase** (via Embase.com interface) using the following search strategy: 1. 'faintness'/exp OR syncope:ab,ti OR fainting:ab,ti OR faintness:ab,ti OR 'tilt-table test':ab,ti 2. 'drinking'/exp OR 'water'/exp OR drinking:ab,ti OR water:ab,ti 3. 1 AND 2 Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in MEDLINE (via PubMed interface).
Search date	10 August 2015
In/Exclusion criteria	**Population**: Include: people with syncope, healthy people with induced syncope (tilt-table testing; description of orthostatic challenge required in methodology); Exclude: patients with autonomic failure, neurogenic orthostatic hypotension, idiopathic orthostatic hypotension, critically ill patients, cardiac patients, blood donors

	Intervention: Include: drinking immediately before fainting (short term intervention); Exclude: drinking habits on a longer term, as a therapy or prophylaxis for syncope **Comparison**: Include: no drinking **Outcome**: Include: blood pressure, time to presyncope **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Claydon, 2006, Germany	Experimental: non-randomized controlled trial (within subjects design)	9 patients with posturally related syncope undergoing tilting All patients had experienced at least one attack of posturally related syncope in the 6 months prior to investigation The patients underwent head-up tilting to an angle of 60° for 20 min.	Ingestion of 500 ml vs 50 ml as a control 15 min before tilting	
Lu, 2003, USA	Experimental: randomized controlled trial (within subjects design)	22 healthy subjects undergoing tilt-table testing Head-up tilt was stepwise (0°, 15°, 30°, 45°, 60°) at 3-minute intervals. Subjects then remained tilted for 45 minutes or until presyncope symptoms were observed.	16 oz (473 mL) of water drinking 5 minutes before tilt-table testing vs tilt-table testing alone Each subject underwent the study protocol twice on separate days.	Subjects were placed on a calculated diet containing 150 mmol sodium and 70 mmol potassium for ≥ 3 days before testing. The volunteers took no food or beverage from midnight until the testing session on the subsequent morning.
Schroeder, 2002, Germany	Experimental: randomized controlled trial (within subjects design)	13 healthy subjects who underwent the head-up tilt test with no history of syncope and on no prescription or over-the-counter medication	ingestion of 500 mL vs 50 mL of mineral water 15 minutes before head-up tilt on two separate days	

		After drinking subjects were tilted back and remained supine for 15 minutes.		

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Orthostatic tolerance (time to presyncope, min)	500 ml vs 50 ml water 15 min before tilting	Statistically significant: 25.4±1.5 vs 19.8±2.3 £ MD: 5.6 (p<0.02) *In favour of water drinking*	1, 9 vs 9 § (within subjects design)	Claydon, 2006
	473 ml of water drinking 5 min before tilting vs no water	Statistically significant: 41.1±8.1 vs 32.6±14.3 MD: 8.5, 95%CI [2.3;14.7] (p=0.011) *In favour of water drinking*	1, 22 vs 22 § (within subjects design)	Lu, 2003
	500 ml vs 50 ml water 15 min before tilting	Statistically significant: 36±3 vs 31±3 £ MD: 5±1 (range -1 to +11) (p<0.001) *In favour of water drinking*	1, 13 vs 13 § (within subjects design)	Schroeder, 2002

Mean ± SD
£ No effect size and CI available
§ Imprecision (limited sample size)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Claydon, 2006	Yes (no randomization)	No	No	No	Within subjects design
Lu, 2003	Unclear (no information about randomization)	No	No	No	Within subjects design
Schroeder, 2002	Unclear (no information about randomization)	No	No	No	Within subjects design

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion(s)	There is limited evidence in favour of water drinking. It was shown that drinking 500 ml resulted in a statistically significant increased orthostatic tolerance compared to no water drinking (Claydon 2006, Lu 2003, Schroeder 2002). Evidence is of low quality and results cannot be considered precise due to limited sample size.
Reference(s)	**Articles** Claydon VE, Schroeder C, Norcliffe LJ, Jordan J, Hainsworth R. *Water drinking improves orthostatic tolerance in patients with posturally related syncope*. Clin Sci (Lond) 2006, 110(3):343-52

	Lu CC, Diedrich A, Tung CS, Paranjape SY, Harris PA, Byrne DW, Jordan J, Robertson D. *Water ingestion as prophylaxis against syncope*. Circulation 2003, 108(21):2660-5 Schroeder C, Bush VE, Norcliffe LJ, Luft FC, Tank J, Jordan J, Hainsworth R. *Water drinking acutely improves orthostatic tolerance in healthy subjects*. Circulation 2002, 106(22):2806-11

Syncope – Posture (Prevention)

Question (PICO)	In humans (P), is a specific posture (such as standing, squatting) (I) compared to another posture (C) effective to prevent syncope (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Syncope"] OR syncope:ti,ab OR fainting:ti,ab OR faintness:ti,ab OR "tilt-table test" 2. [mh "posture"] OR posture:ti,ab OR squatting:ti,ab OR standing:ti,ab 3. prevent*:ti,ab 4. 1-3 AND **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Syncope"[Mesh] OR syncope[TIAB] OR fainting[TIAB] OR faintness[TIAB] OR "Tilt-Table Test"[Mesh] 2. "Posture"[Mesh] OR posture[TIAB] OR squatting[TIAB] OR standing[TIAB] 3. "Primary Prevention"[Mesh:NoExp] OR "Health Education"[Mesh] OR "Health Behavior"[Mesh:NoExp] OR "Preventive Medicine"[Mesh] OR "Prevention and control "[Subheading] OR prevent*[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'faintness'/exp OR syncope:ab,ti OR fainting:ab,ti OR faintness:ab,ti OR 'tilt-table test':ab,ti 2. 'body posture'/exp OR posture:ab,ti OR squatting:ab,ti OR standing:ab,ti 3. 'prevention'/exp OR 'health education'/exp OR 'health behavior'/exp OR 'self examination'/de OR 'preventive medicine'/exp OR *'prevention':lnk OR* 'risk factor'/exp OR prevent*:ab,ti 4. 1-3 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in MEDLINE (via PubMed interface).
Search date	17 August 2015
In/Exclusion criteria	**Population**: Include: people with syncope, healthy people with induced syncope (tilt-table testing; description of orthostatic challenge required in methodology); Exclude: patients with autonomic failure, neurogenic orthostatic hypotension, idiopathic orthostatic hypotension, critically ill patients, cardiac patients, blood donors **Intervention**: Include: a specific body posture such as squatting or standing; Exclude: physical manoeuvres such as leg crossing, muscle tensing (other PICO) **Comparison**: Include: another body posture **Outcome**: Include: blood pressure, time to presyncope **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available.

	An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: conference abstracts, case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Kim, 2005, Korea	Experimental: non-randomized controlled trial (within subjects design)	50 patients who underwent the head-up tilt (HUT) test (27 patients with positive HUT, 23 patients with negative HUT); 21 control subjects Patients were tilted to 60° for 20 min. [only data of patients with positive HUT test and control subjects were extracted]	1. squatting 2. leg-crossing with muscle tensing 3. handgrip 4. normal standing Maneuvers were performed for 30 s, 5 min before and after HUT. [only data concerning squatting and normal standing were extracted]	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Blood pressure	Squatting vs normal standing	Systolic (change): Statistically significant: *Patients* Before HUT: 7.1±5.1 £† (p<0.05) After HUT: 14.8±15.7 £† (p<0.05) *Healthy people* Before HUT: 6.5±5.0 £† (p<0.05) After HUT: 9.1±7.1 £† (p<0.05) Diastolic: *Patients* Before HUT: 4.6±5.8 £† (p<0.05) After HUT: 8.4±10.1 £† (p<0.05) *Healthy people* Before HUT: 3.7±3.9 £† (p<0.05) After HUT: 6.8±7.3 £† (p<0.05) *In favour of squatting*	1, 48 vs 48 § (within subjects design)	Kim, 2005

Mean Difference ± SD

£ No raw data/CI available

§ Imprecision (limited sample size or low number of events)

† Imprecision (lack of data)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Kim, 2005	Yes (no randomization)	Unclear	No	No	Within subjects design

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes, lack of data
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion(s)	There is limited evidence in favour of squatting. It was shown that squatting resulted in a statistically significant increase of systolic and diastolic blood pressure, compared to normal standing (Kim 2005). Evidence is of low quality and results cannot be considered precise due to limited sample size and lack of data.
Reference(s)	**Articles** Kim KH, Cho JG, Lee KO, Seo TJ, Shon CY, Lim SY, Yun KH, Sohn IS, Hong YJ, Park HW, Kim JH, Kim W, Ahn YK, Jeong MH, Park JC, Kang JC. *Usefulness of physical maneuvers for prevention of vasovagal syncope*. Circ J 2005, 69(9):1084-8

Syncope – Physical manoeuvres (Prevention)

Question (PICO)	In humans (P), are certain physical manoeuvres (I) compared to other physical manoeuvres (C) more effective to prevent syncope (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Syncope"] OR syncope:ti,ab OR fainting:ti,ab OR faintness:ti,ab OR "tilt-table test" 2. [mh "posture"] OR posture:ti,ab OR "leg crossing":ti,ab OR (muscle NEXT tens*):ti,ab OR arm:ab,ti 3. prevent*:ti,ab 4. 1-3 AND **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Syncope"[Mesh] OR syncope[TIAB] OR fainting[TIAB] OR faintness[TIAB] OR "Tilt-Table Test"[Mesh] 2. "Posture"[Mesh] OR posture[TIAB] OR (leg*[TIAB] AND cross*[TIAB]) OR muscle tens*[TIAB] OR arm[TIAB] 3. "Primary Prevention"[Mesh:NoExp] OR "Health Education"[Mesh] OR "Health Behavior"[Mesh:NoExp] OR "Preventive Medicine"[Mesh] OR "Prevention and control "[Subheading] OR prevent*[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'faintness'/exp OR syncope:ab,ti OR fainting:ab,ti OR faintness:ab,ti OR 'tilt-table test':ab,ti 2. 'body posture'/exp OR posture:ab,ti OR (leg*:ab,ti AND cross*:ab,ti) OR (muscle NEXT/1 tens*):ab,ti OR arm:ab,ti

	3. 'prevention'/exp OR 'health education'/exp OR 'health behavior'/exp OR 'self examination'/de OR 'preventive medicine'/exp OR *'prevention':lnk OR* 'risk factor'/exp OR prevent*:ab,ti 4. 1-3 AND Systematic review, retrieved with the above searches, and used as source for individual studies: Pauwels, 2012; no update of individual studies for leg crossing was made (however an update was made for other physical manoeuvres such as arm exercise and muscle tensing); only studies that fulfilled our selection criteria were extracted from this review. Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in MEDLINE (via PubMed interface).
Search date	18 August 2015
In/Exclusion criteria	**Population**: Include: people with (recurrent episodes of) syncope, healthy people with induced syncope (tilt-table testing; description of orthostatic challenge required in methodology); Exclude: patients with autonomic failure, neurogenic orthostatic hypotension, idiopathic orthostatic hypotension, critically ill patients, cardiac patients, blood donors **Intervention**: Include: a specific physical manoeuvre, including leg crossing, muscle tensing, arm exercise **Comparison**: Include: another physical manoeuvre or no intervention **Outcome**: Include: blood pressure, time to presyncope **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: conference abstracts, case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Brignole, 2002, Italy	Experimental: randomized controlled trial (within subjects design)	19 patients affected by tilt-induced vasovagal syncope	1. handgrip for 2 min, starting at the time of onset of symptoms of impending syncope 2. no handgrip Arm-tensing consisted of the maximum tolerated isometric contraction of the two arms achieved by gripping one hand with the other and contemporarily abducting (pushing away) the arms.	The Italian tilt protocol, namely 60° passive tilting followed by 0.4 mg nitro-glycerine challenge when the passive phase fails to induce syncope, was used.

Groothuis, 2007, The Netherlands	Experimental: non-randomized controlled trial (within subjects design)	13 healthy subjects (age 23.6 yr ± 1.0) (mean ± SEM) After 10 min in the supine position subjects were tilted manually within 5 s to 70° head-up tilt for 10 min.	1. leg crossing with muscle tension 2. standing The physical counter-manoeuvre was executed within 2 s and continued for 2 min.	
Kim, 2005, Korea	Experimental: non-randomized controlled trial (within subjects design)	50 patients who underwent the head-up tilt (HUT) test (27 patients with positive HUT, 23 patients with negative HUT); 21 control subjects [only data of patients with positive HUT test and control subjects were extracted]	1. squatting 2. leg-crossing with muscle tensing 3. handgrip 4. normal standing Manoeuvres were performed for 30 s, 5 min before and after HUT. [data concerning squatting were not extracted (other PICO)]	Patients were tilted to 60° for 20 min.
Krediet, 2002, The Netherlands	Experimental: non-randomized controlled trial (within subjects design)	21 patients with vasovagal syncope (mean age 41 yr [Range: 17 – 74])	1. leg crossing with muscle tension 2. standing The manoeuvre consists of crossing the legs in standing position with tensing of leg, abdominal, and buttock muscles. The legs are thus firmly squeezed together. Participants were asked to uncross their legs after at least 30 seconds following the disappearance of prodromal symptoms.	The tilt-table test started with 5 minutes of supine rest. The subjects were then tilted head up (60 degrees) for 20 minutes. If no Vaso-vagal faint developed, nitroglycerin was administrated sublingually (0.4 mg) before an additional 15-minute tilt.
Krediet, 2006, The Netherlands	Experimental: randomized controlled trial (within subjects design)	9 healthy subjects (median age: 25 yr [range: 20 - 41]) subjected to the induction of presyncope via head-up tilting with incremental lower body negative pressure	1. leg crossing 2. standing When testing leg crossing, this manoeuvre commenced 3 min after onset of tilt.	After a 5-min supine baseline period, subjects were 60° head-up tilted.
Krediet, 2008, The Netherlands	Experimental: non-randomized controlled trial (within subjects design)	18 patients with recurrent syncope	1. standing after squatting + lower body muscle tensing 2. standing after squatting After 5 min of standing, participants squatted for 1 min and then rose within 1 second and stood for	After 5 minutes of supine rest, patients were 60° head-up tilted for 20 minute. If no vasovagal reaction developed,

			another 1 min. After tilting they performed two squat manoeuvres. Squatting was performed for 1 min. Immediately thereafter they performed lower body muscle tensing for 30–40 seconds, which consisted of the tensing of all skeletal muscles in the abdomen, buttocks and legs at maximal voluntary capacity.	0.4 mg nitro-glycerine was administrated sublingually prior to an additional 15 minute tilt.
Van Dijk, 2005, The Netherlands	Experimental: non-randomized controlled trial (within subjects design)	88 patients with vasovagal syncope (median age 38.5 yr [range: 16 - 85])	1. leg crossing with muscle tension 2. standing After 5 min of supine rest, patients were asked to stand up and remain standing for 5 min. Patients were then instructed to cross their legs and stand firmly on both legs for 2 min. After this 2-min period, patients tensed the skeletal muscles of the legs, abdomen, and buttocks firmly for 1 more min, while in the legs-crossed position.	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Leg crossing (+ muscle tension)				
Orthostatic tolerance (min) (Mean ± SEM)	Leg crossing vs standing	Statistically significant: 34 ± 2 vs 26 ± 2 £† MD: 8 (p<0.001) *In favour of leg crossing*	1, 9 vs 9 § (within subjects design)	Krediet, 2006
Blood pressure (mm Hg)		Not statistically significant: Systolic: 81 ± 4 mm Hg vs 72 ± 7 (mean ± SEM) £† MD: 9 Diastolic: 55 ± 2 mm Hg vs 48 ± 5 mm Hg (mean ± SEM) £† MD: 7		
	Leg crossing + muscle tension vs standing	Statistically significant: 102.5 ± 3.4 vs. 89.3 ± 2.5 (mean ± SEM) £† MD: 13.2 (p<0.05) *In favour of leg crossing and muscle tension*	1, 13 vs 13 § (within subjects design)	Groothuis, 2007
		Systolic (change): Statistically significant: Patients before HUT: 8.0 ± 5.8 £† (p<0.05) Patients after HUT: 13.9±16.9 £† (p<0.05)	1, 48 vs 48 § (within subjects design)	Kim, 2005

		Healthy subjects before HUT: 8.7 ± 5.7 £† (p<0.05) Healthy subjects after HUT: 4.5±6.4 £† (p<0.05) *In favour of leg crossing and muscle tension* Diastolic (change): Statistically significant: Patients after HUT: 6.4±10.1 £† (p<0.05) *In favour of leg crossing and muscle tension* Not statistically significant: Patients before HUT: 1.6 ± 4.8 £† Healthy subjects before HUT: 1.1 ± 4.9 £† Healthy subjects after HUT: 2.1±2.4 £†		
		Statistically significant: Systolic: 106 ± 16 vs 65 ± 13 £† MD: 41 (p<0.001) Diastolic: 65 ± 10 vs 43 ± 9 £† MD: 22 (p<0.001) *In favour of leg crossing and muscle tension*	1, 21 vs 21 § (within subjects design)	Krediet, 2002
		Statistically significant: Systolic: 130.9 ± 16.9 vs 125.3 ± 16.1 £† MD: 5.6 (p<0.001) Diastolic: 75.0 ± 10.7 vs 73.8 ± 10.3 £† MD: 1.2 (p<0.01) *In favour of leg crossing and muscle tension*	1, 88 vs 88 § (within subjects design)	Van Dijk, 2005
Arm exercise				
Blood pressure	Handgrip/arm exercise vs no exercise	Statistically significant: Systolic: 105±38 vs 73±21 MD: 32 (p=0.008) Diastolic: 71±24 vs 51±20 (p=0.004) *In favour of arm exercise*	1, 19 vs 19 § (within subjects design)	Brignole, 2002
		Systolic (change): Not statistically significant: Patients before HUT: 2.1±4.7 £† Patients after HUT: 2.3±8.9 £† Healthy subjects before HUT: 1.5±5.3 £† Healthy subjects after HUT: 2.5±9.7 £† Diastolic (change): Statistically significant: Patients after HUT: 5.1±10.8 £† (p<0.05) *In favour of handgrip* Not statistically significant: Patients before HUT: 1.6±8.2 £†	1, 48 vs 48 § (within subjects design)	Kim, 2005

		Healthy subjects before HUT: 0.3±5.9 £† Healthy subjects after HUT: 0.6±9.9 £†		
Muscle tensing				
Persisting pre-syncopal symptoms	standing after squatting + lower body muscle tensing vs standing after squatting	<u>Statistically significant:</u> 2/18 vs 13/18 RR: 0.15 (p<0.001) *In favour of standing after squatting and lower body muscle tension*	1, 18 vs 18 § (within subjects design)	Krediet, 2008
Mean arterial blood pressure		<u>Statistically significant</u>: 76±3 vs 64±4 MD: 12 (p<0.001) *In favour of standing after squatting and lower body muscle tension*		

Mean ± SD (unless otherwise indicated)
£ No effect size and CI available
§ Imprecision (limited sample size)
† Imprecision (lack of data)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Brignole, 2002	Yes (not possible to conceal allocation to participants)	Unclear	No	No	Within subjects design
Groothuis, 2007	Yes (no randomization)	Unclear	No	No	Within subjects design
Kim, 2005, Korea	Yes (no randomization)	Unclear	No	No	Within subjects design
Krediet, 2002	Yes (no randomization)	Unclear	No	No	Within subjects design
Krediet, 2006	Yes (not possible to conceal allocation to participants)	Unclear	No	No	Within subjects design
Krediet, 2008	Yes (no randomization)	Unclear	No	No	Within subjects design
Van Dijk, 2005	Yes (no randomization)	Unclear	No	No	Within subjects design

Level of evidence

Leg crossing (+ muscle tension)

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes, lack of data
Inconsistency	0	
Indirectness	-1	1 study with healthy subjects; majority of studies measures indirect outcomes
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Handgrip/arm exercise

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes, lack of data
Inconsistency	0	
Indirectness	-1	Indirect outcome
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Muscle tension

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes, lack of data
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion(s)	**Leg crossing (+ muscle tension)** There is limited evidence in favour of leg crossing with or without muscle tension. It was shown that leg crossing resulted in a statistically significant improved orthostatic tolerance compared to standing (Krediet 2006). However, a statistically significant increase of blood pressure in case of leg crossing compared to standing could not be demonstrated (Krediet 2006). It was shown that leg crossing combined with muscle tensing resulted in a statistically significant increased systolic blood pressure compared to standing, however, an increased diastolic blood pressure could not be demonstrated (Groothuis 2007, Kim 2005, Krediet 2002, Van Dijk 2005). Evidence is of very low quality and results cannot be considered precise due to limited sample size and lack of data. **Arm exercise** There is limited evidence in favour of arm exercise. It was shown that arm exercise resulted in a statistically significant increased diastolic blood pressure compared to no arm exercise, however, a consistent increased diastolic blood pressure could not be demonstrated (Brignole 2002, Kim 2005). Evidence is of very low quality and results cannot be considered precise due to limited sample size and lack of data. **Muscle tension** There is limited evidence in favour of muscle tension. It was shown that standing after squatting followed by lower body muscle tensing resulted in a statistically significant decrease of persisting pre-syncopal symptoms and increase of mean arterial blood pressure compared to standing after squatting alone (Krediet 2008). Evidence is of low quality and results cannot be considered precise due to limited sample size and lack of data.
Reference(s)	**Articles** Brignole M, Croci F, Menozzi C, Solano A, Donateo P, Oddone D, Puggioni E, Lolli G. *Isometric arm counter-pressure maneuvers to abort impending vasovagal syncope*. J Am Coll Cardiol 2002, 40(11):2053-9 Groothuis JT, van DN, Ter WW, Wieling W, Hopman MT. *Leg crossing with muscle tensing, a physical counter-manoeuvre to prevent syncope, enhances leg blood flow*. Clin Sci (Lond) 2007, 112(3):193-201 Kim KH, Cho JG, Lee KO, Seo TJ, Shon CY, Lim SY, Yun KH, Sohn IS, Hong YJ, Park HW, Kim JH, Kim W, Ahn YK, Jeong MH, Park JC, Kang JC. *Usefulness of physical maneuvers for prevention of vasovagal syncope*. Circ J 2005, 69(9):1084-8

	Krediet CT, van DN, Linzer M, van Lieshout JJ, Wieling W. *Management of vasovagal syncope: controlling or aborting faints by leg crossing and muscle tensing*. Circulation 2002, 106(13):1684-9 Krediet CT, van Lieshout JJ, Bogert LW, Immink RV, Kim YS, Wieling W. *Leg crossing improves orthostatic tolerance in healthy subjects: a placebo-controlled crossover study*. Am J Physiol Heart Circ Physiol 2006, 291(4):H1768-H1772 Krediet CT, Go-Schön IK, van Lieshout JJ, Wieling W. *Optimizing squatting as a physical maneuver to prevent vasovagal syncope*. Clin Auton Res 2008, 18(4):179-86 van Dijk N, de Bruin IG, Gisolf J, de Bruin-Bon HA, Linzer M, van Lieshout JJ, Wieling W. *Hemodynamic effects of leg crossing and skeletal muscle tensing during free standing in patients with vasovagal syncope*. J Appl Physiol 2005, 98(2):584-90

Head injury – Clinical signs/symptoms (Diagnostics)

Question (PICO)	Among persons (P), are some symptoms (I) more predictive than others (C) for the diagnosis of a head injury (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. MeSH descriptor: [head injuries, closed] explode all trees OR MeSH descriptor: [head injuries,penetrating] explode all trees OR MeSH descriptor: [intracranial hemorrhage,traumatic] explode all trees OR MeSH descriptor: [brain injuries] explode all trees OR 'head injury':ti,ab,kw OR 'head injuries':ti,ab,kw OR 'head trauma':ti,ab,kw 2. MeSH descriptor: [sensitivity and specificity] explode all trees OR MeSH descriptor: [predictive value of tests] explode all trees OR MeSH descriptor: [reference values] explode all trees OR MeSH descriptor: [roc curve] explode all trees OR 'sensitivity':ti,ab,kw OR 'specificity':ti,ab,kw OR 'false positive':ti,ab,kw OR 'false negative':ti,ab,kw OR 'accuracy':ti,ab,kw OR 'predictive value':ti,ab,kw OR 'reference value':ti,ab,kw OR 'reference standard':ti,ab,kw OR 'roc':ti,ab,kw OR 'likelihood ratio':ti,ab,kw 3. signs:ti,ab,kw OR sign:ti,ab,kw OR symptom*:ti,ab,kw 4. MeSH descriptor: [meta-analysis] explode all trees OR meta analys*:ti,ab,kw OR meta-analys*:ti,ab,kw OR 'cochrane':ti,ab,kw OR 'embase':ti,ab,kw OR 'pubmed':ti,ab,kw OR 'medline':ti,ab,kw OR 'reference list':ti,ab,kw OR 'reference lists':ti,ab,kw OR 'bibliography':ti,ab,kw OR 'bibliographies':ti,ab,kw OR 'hand-search':ti,ab,kw OR 'manual search':ti,ab,kw OR 'selection criteria':ti,ab,kw OR 'relevant journals':ti,ab,kw 5. 1-4 AND **MEDLINE** (via PubMed interface) for guidelines and systematic reviews using the following search strategy: 1. "head injuries,closed"[Mesh] OR "head injuries,penetrating"[Mesh] OR "intracranial hemorrhage, traumatic"[Mesh] OR "brain injuries"[Mesh] OR "head injury"[TIAB] OR "head injuries"[TIAB] OR "head trauma"[TIAB] 2. signs[tiab] OR sign[tiab] OR symptom*[tiab] 3. "sensitivity and specificity"[Mesh] OR "sensitivity"[TIAB] OR "specificity"[TIAB] OR "predictive value of tests"[Mesh] OR "false positive"[TIAB] OR "false negative"[TIAB] OR "accuracy"[TIAB] OR "predictive value"[TIAB] OR "reference values"[Mesh] OR "reference value"[TIAB] OR"reference standard"[TIAB] OR "roc curve"[Mesh] OR "roc"[TIAB] OR "likelihood ratio"[TIAB] 4. "guideline "[Publication Type] OR "Practice Guidelines as Topic"[Mesh] OR "Practice Guideline "[Publication Type] OR practice guideline*[TIAB])) OR Meta-Analysis as Topic[Mesh] OR meta analy*[TIAB] OR metaanaly*[TIAB] OR Meta-Analysis[Publication Type] OR systematic review*[TIAB] OR systematic

	overview*[TIAB] OR Review Literature as Topic[Mesh] OR cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB]))) OR reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB] OR selection criteria[TIAB] OR data extraction[TIAB] 5. 1-4 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'head injury'/exp OR 'brain hemorrhage'/exp OR 'traumatic brain injury'/exp OR 'head injury':ab,ti OR 'head injuries':ab,ti OR 'head trauma':ab,ti 2. 'signs':ab,ti OR 'sign':ab,ti OR symptom*:ab,ti 3. 'sensitivity and specificity'/exp OR 'sensitivity':ab,ti OR 'specificity':ab,ti OR 'false positive':ab,ti OR 'false negative':ab,ti OR 'diagnostic accuracy'/exp OR 'accuracy':ab,ti OR 'predictive value'/exp OR 'predictive value':ab,ti OR 'reference value'/exp OR 'reference value':ab,ti OR 'reference standard':ab,ti OR 'receiving operator characteristic'/exp OR 'receiver operating characteristic':ab,ti OR 'roc':ab,ti OR 'likelihood ratio':ab,ti 4. 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti 5. 1-4 AND Guideline, retrieved with the above searches, and used as source for individual studies: NICE 2014
Search date	01 March 2015
In/Exclusion criteria	**Population:** Include: infants, children or adults that have an acute traumatic head injury (closed/penetrated/intracranial). Exclude: infants, children or adults with head injuries not caused by an acute traumatic event (e.g. stroke). Spinal injuries were excluded. **Intervention:** Include: clinical symptoms/signs suggestive for an acute traumatic head injury which can be detected by lay people (i.e. basic first responders, lay caregivers and/or community health workers). Only symptoms with data for a 2x2 table were considered Exclude: clinical symptoms suggestive for an acute traumatic head injury which cannot be detected by lay people. **Comparison:** Include: a diagnostic reference method for the diagnosis of an acute traumatic head injury (e.g. imaging) Exclude: studies not using a diagnostic reference method. **Outcome:** Include: Patient-important outcomes (i.e. survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects)) or accuracy-related outcomes such as sensitivity, specificity and/or positive/negative likelihood ratio (pLR/nLR). Likelihood ratios were considered as the preferred measure of diagnostic accuracy since they are clinically more meaningful than sensitivities, specificities, or diagnostic odds ratios. They quantify how strongly the likelihood of a disease is changed by the presence (pLR) or absence (nLR) of a symptom or sign. A LR of 1 indicates a test result without any diagnostic value. LRs of 1 to 2 or 0.5 to 1 change the likelihood very little and they are rarely important. LRs ≤0.5 or ≥2 change it at least moderately and can be considered as clinically helpful in the context of medical history taking and physical examination. If no information on likelihood ratios is reported, data of sensitivity and specificity are extracted. **Study design:** Include: a systematic review (of diagnostic accuracy studies) was included if the search strategy and selection criteria are clearly described and if at least MEDLINE and one other relevant database was searched. If no systematic review was published within the last 5 years, a search for individual diagnostic accuracy studies was performed. Exclude: case series**,** animal studies, *ex vivo* or *in vitro* studies.

	Language: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline)

Characteristics of included studies

In the NICE guideline from 2014 it is stated that no studies with patients with moderate or severe head injury were identified.

Author, year, Country	Study design	Population	Comparison	Remarks
Pandor, 2011, United Kingdom	Systematic review of 93 diagnostic accuracy studies	Adults and children with minor head injury (defined as patients with a blunt head injury and a Glasgow Coma Scale score of 13–15 at presentation). Studies of patients with moderate or severe head injury (defined as patients with a GCS of ≤ 12 at presentation) or no history of injury were excluded. Studies that recruited patients with a broad range of head injury severity were included only if > 50% of the patients had minor head injury.	Index test (symptom): - dizziness - visual symptoms - any loss of consciousness - any headache - severe or persistent headache - undefined vomiting - persistent vomiting - undefined or mixed amnesia - anterograde or post-trauma amnesia - scalp laceration - scalp haematoma Reference standard: imaging (CT scan or MRI scan)	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Infants				
Diagnosis intracranial injury (defined as any intracranial abnormality detected on CT or MRI scan due to trauma): positive likelihood ratio	Any seizure versus reference standard	LR+ 1.32, 95% CI [0.23 to 7.55]	2, #participants not reported per comparison (diagnostic accuracy study)	Pandor, 2011
	Any loss of consciousness versus reference standard	LR+ 2.51, 95% CI [1.23 to 5.28] *index test can be considered as clinically helpful for the presence of intracranial injury*	4, #participants not reported per comparison (diagnostic accuracy study)	
	Undefined vomiting versus reference standard	LR+ 0.67, 95% CI [0.12 to 3.65]	2, #participants not reported per comparison (diagnostic accuracy study)	
	Persistent vomiting versus reference standard	LR+ 1.00, 95% CI [0.30 to 3.37]	1, #participants not reported per comparison (diagnostic accuracy study)	
	Scalp haematoma versus reference standard	LR+ 1.51, 95% CI [1.33 to 1.73]	2, #participants not reported per comparison (diagnostic accuracy study)	
Children				
Diagnosis intracranial injury (defined as any intracranial	Dizziness versus reference standard	LR+ 0.79, 95% CI [0.11 to 4.30]	3, #participants not reported per comparison (diagnostic accuracy study)	Pandor, 2011

abnormality detected on CT or MRI scan due to trauma): positive likelihood ratio	Any seizure versus reference standard	LR+ 2.69, 95% CI [1.17 to 6.24] *index test can be considered as clinically helpful for the presence of intracranial injury*	9, #participants not reported per comparison (diagnostic accuracy study)	
	Visual symptoms versus reference standard	LR+ 3.51, 95% CI [1.63 to 7.57] *index test can be considered as clinically helpful for the presence of intracranial injury*	2, #participants not reported per comparison (diagnostic accuracy study)	
	Any loss of consciousness versus reference standard	LR+ 2.30, 95% CI [1.46 to 3.47] *index test can be considered as clinically helpful for the presence of intracranial injury*	17, #participants not reported per comparison (diagnostic accuracy study)	
	Any headache versus reference standard	LR+ 1.26, 95% CI [0.97 to 1.61]	14, #participants not reported per comparison (diagnostic accuracy study)	
	Severe or persistent headache versus reference standard	LR+ 4.35, 95% CI [1.07 to 12.35] *index test can be considered as clinically helpful for the presence of intracranial injury*	5, #participants not reported per comparison (diagnostic accuracy study)	
	Undefined vomiting versus reference standard	LR+ 1.29, 95% CI [0.85 to 1.99]	14, #participants not reported per comparison (diagnostic accuracy study)	
	Persistent vomiting	LR+ 3.14, 95% CI [1.30 to 8.05] *index test can be considered as clinically helpful for the presence of intracranial injury*	4, #participants not reported per comparison (diagnostic accuracy study)	
	Undefined or mixed amnesia	LR+ 1.82, 95% CI [1.00 to 3.74]	8, #participants not reported per comparison (diagnostic accuracy study)	
	Anterograde or post-trauma amnesia versus reference standard	LR+ 2.97, 95% CI [1.40 to 6.29] *index test can be considered as clinically helpful for the presence of intracranial injury*	1, #participants not reported per comparison (diagnostic accuracy study)	
	Scalp laceration versus reference standard	LR+ 0.67, 95% CI [0.02 to 2.27]	3, #participants not reported per comparison (diagnostic accuracy study)	
	Scalp haematoma versus reference standard	LR+ 1.70, 95% CI [1.30 to 2.23] *index test can be considered as not clinically helpful for the presence of intracranial injury*	5, #participants not reported per comparison (diagnostic accuracy study)	
Adults				
Diagnosis intracranial injury (defined as any intracranial abnormality detected on CT or MRI scan due to trauma): positive likelihood ratio	Dizziness versus reference standard	LR+ 0.72, 95% CI [0.44 to 1.09]	3, #participants not reported per comparison (diagnostic accuracy study)	Pandor, 2011
	Any seizure versus reference standard	LR+ 2.59, 95% CI [1.20 to 6.40] *index test can be considered as clinically helpful for the presence of intracranial injury*	10, #participants not reported per comparison (diagnostic accuracy study)	
	Visual symptoms versus reference standard	LR+ 0.39, 95% CI [0.00 to 2.49] *index test can be considered as clinically helpful for the absence of intracranial injury*	3, #participants not reported per comparison (diagnostic accuracy study)	

	Any loss of consciousness versus reference standard	LR+ 1.41, 95% CI [1.14 to 1.84]	17, #participants not reported per comparison (diagnostic accuracy study)	
	Any headache versus reference standard	LR+ 1.23, 95% CI [0.99 to 1.55]	13, #participants not reported per comparison (diagnostic accuracy study)	
	Severe or persistent headache versus reference standard	LR+ 1.00, 95% CI [0.86 to 1.16]	2, #participants not reported per comparison (diagnostic accuracy study)	
	Undefined vomiting versus reference standard	LR+ 2.58, 95% CI [1.52 to 4.49] *index test can be considered as clinically helpful for the presence of intracranial injury*	10, #participants not reported per comparison (diagnostic accuracy study)	
	Persistent vomiting versus reference standard	LR+ 5.53, 95% CI [1.33 to 30.12] *index test can be considered as clinically helpful for the presence of intracranial injury*	4, #participants not reported per comparison (diagnostic accuracy study)	
	Retrograde amnesia versus reference standard	LR+ 2.41, 95% CI [1.21 to 4.55] *index test can be considered as clinically helpful for the presence of intracranial injury*	4, #participants not reported per comparison (diagnostic accuracy study)	
	Undefined or mixed amnesia	LR+ 1.27, 95% CI [0.98 to 1.59]	7, #participants not reported per comparison (diagnostic accuracy study)	
	Anterograde or post-traumatic amnesia	LR+ 1.95, 95% CI [1.48 to 2.62]	6, #participants not reported per comparison (diagnostic accuracy study)	

LR+: positive likelihood ratio

Quality of evidence

Author, Year	Information about 'limitations of study design' from the SR
Pandor, 2011	**Adults** Overall, most of the included studies were well reported and generally satisfied the majority of the quality assessment items of the QUADAS tool, but with notable exceptions. Despite poor reporting of the reference standards in most studies, the main source of variation was for patient spectrum, which will affect comparability across cohorts and application of conclusions to practice. **Children and infants** Overall, most of the included studies were poorly reported and did not satisfy the majority of the quality assessment items of the QUADAS tool. The study that scored the most negatives and fewest positives was also one of the two large cohorts (> 20,000), and consequently has the potential to influence the results. This study scored poorly mainly owing to the use of pragmatic reference standards.

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	0	
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Moderate [B]**	

Conclusion	**Infants** There is limited evidence showing that any loss of consciousness is a predictive symptom for the presence of a minor intracranial head injury (Pandor 2011). Evidence is of moderate quality. **Children** There is limited evidence showing that any seizure, visual symptoms, any loss of consciousness, severe or persistent headache, persistent vomiting, anterograde or post-trauma amnesia are predictive symptoms for the presence of a minor intracranial head injury (Pandor 2011). Evidence is of moderate quality. **Adults** There is limited evidence showing that any seizure, undefined/persistent vomiting or retrograde amnesia are predictive symptoms for the presence of a minor intracranial head injury. Visual symptoms could be considered as clinically helpful for the absence of a minor intracranial head injury (Pandor 2011). Evidence is of moderate quality.
Reference(s)	**Articles** Pandor A, Goodacre S, Harnan S, Holmes M, Pickering A, Fitzgerald P, Rees A, Stevenson M. *Diagnostic management strategies for adults and children with minor head injury: a systematic review and an economic evaluation.* Health Technol Assess 2011, 15(27):1-202. **Guidelines** NICE 2014. *Head injury: Triage, assessment, investigation and early management of head injury in children, young people and adults*.

Head injury – Bicycle helmet (Prevention)

Question (PICO)	In bicyclists (P), is using a bicycle helmet (I) effective to prevent head injury (O) compared to not using a helmet (C)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Craniocerebral trauma"] OR "head injury":ti,ab 2. [mh "Head Protective Devices"] OR helmet*:ti,ab 3. 1 AND 2 A Cochrane systematic review of 2009 was included. This review was not updated, because of the large and consistent evidence base in favour of bicycle helmets.
Search date	20 August 2015
In/Exclusion criteria	**Population**: Include: adults and children, bicyclists **Intervention**: Include: use of bicycle helmet **Comparison**: Include: not using a helmet **Outcome**: Include: head injury **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched.

	An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: conference abstracts, case series, cross-sectional studies (studies collecting information concerning type of car and injury in health insurance companies), animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline)

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Thompson, 1999, USA	Systematic review	5 case-control studies including 7253 bicyclists who had experienced a crash [only 4 of the 5 studies were used by the Cochrane author for the pooled value reported below]	Use of bicycle helmets vs not	Last assessed as up-to-date: 7 November 2006

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Head injury	Helmets for bicyclists vs no head-protecting devices	Statistically significant: No raw data (cases versus controls) available OR= 0.31, 95%CI [0.26;0.37] ($p<0.05$) *In favour of bicycle helmet*	4, 5543 (no separate numbers available for cases and controls)	Thompson 2009

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	0	See systematic review of Thompson 2009
Imprecision	0	
Inconsistency	0	
Indirectness	0	
Publication bias	0	
Very large magnitude of effect	+1	
QUALITY (GRADE)	**Final grading Moderate [B]**	

Conclusion	There is evidence in favour of wearing a bicycle helmet. It was shown that wearing a bicycle helmet resulted in a statistically significant decrease of head injuries, compared to not wearing a helmet (Thompson 2009). Evidence is of moderate quality.
Reference(s)	**Articles** Thompson DC, Rivara F, Thompson R. *Helmets for preventing head and facial injuries in bicyclists*. Cochrane Database of Systematic Reviews 1999, Issue 4.

Fall injuries – Home safety assessment (Prevention)

Question (PICO)	In humans (P), is home safety assessment (I) compared to no home safety assessment (C) effective to prevent falls injuries (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search term: [mh "Accidental falls"] A Cochrane systematic review of 2012 was included. This review was not updated with individual studies.
Search date	21 August 2015
Inclusion/Exclusion criteria	**Population**: Include: people older than 60 **Intervention**: Include: home safety interventions, adaptations to homes, aids or technology to improve home safety; Exclude: medication, education, exercises, therapy **Outcome**: Include: falls, fractures, head injury **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: conference abstracts, case series, cross-sectional studies (studies collecting information concerning type of car and injury in health insurance companies), animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline)

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Gillespie, 2012, UK	Systematic review	159 experimental studies (randomized controlled trials, including 145 studies that were individually randomized (including 1 within subjects design) and 14 studies that were cluster randomized). Studies included older people of 60 years and older. Trials that included younger participants have been included if the mean age minus one standard deviation was more than 60 years. Participants included were living in the community, either at home or in places of residence that, on the whole, do not provide residential health-related care or rehabilitative services.	Interventions to prevent falls, including: -exercises -medication (vitamin D) -surgery (cardiac pacing) -fluid or nutrition therapy -psychological interventions -environment/assistive technology (adaptations to homes/home safety assessment/interventions to improve vision/footwear modification) -knowledge/education interventions [only data concerning environment/assistive technology were extracted (9 different studies)]	Last assessed as up-to-date: 1 March 2012

		70% of included participants were women.		

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Rate of falls	Home safety assessment versus no home safety assessment	Statistically significant: RR: 0.81, 95%CI [0.68;0.97] (p=0.022) £ *In favour of home safety*	6, 1806 vs 2402	Gillespie, 2012
Number of fallers		Statistically significant: RR: 0.88, 95%CI [0.80;0.96] (p=0.0028) £ *In favour of home safety*	7, 1766 vs 2285	
Number of participants sustaining a fracture		Not statistically significant: RR: 1.32, 95%CI [0.30;5.87] ¥ (p=0.71) £	1, 181 vs 179 §	

£ No raw data available

§ Imprecision (low number of participants)

¥ Imprecision (large variability of results)

Quality of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See systematic review
Imprecision	0	
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Moderate [B]**	

Conclusion	There is evidence in favour of home safety assessment (looking for possible risk factors that impair home safety such as uneven or slippery flooring, poor lighting, presence of throw, scatter rug, clutter or electric cords, items that are not reachable). It was shown that home safety assessment resulted in a statistically significant decrease of rate of falls and number of fallers compared to no home safety assessment, however a decrease in the number of participants sustaining a fracture could not be demonstrated (Gillespie 2012). Evidence is of moderate quality.
Reference(s)	**Articles** Gillespie LD, Robertson MC, Gillespie WJ, Sherrington C, Gates S, Clemson LM, Lamb SE. *Interventions for preventing falls in older people living in the community*. Cochrane Database Syst Rev 2012, 9:CD007146

Spine injury – Manual stabilisation using hands or knees (First Aid)

Question (PICO)	In people with spinal injury (I) is manual stabilisation of the head with hands or knees (I) vs not doing this (C) effective to change survival, functional recovery, pain, complications, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the search terms: 1. [mh "Spinal injury"] OR (spine NEXT injur*):ti,ab,kw OR (spinal NEXT injur*):ti,ab,kw OR (cervical NEXT injur*):ti,ab,kw OR (cervical NEXT spine*):ti,ab,kw OR 'cervical vertebrae':ti,ab,kw 2. 'hand':ti,ab,kw OR 'hands':ti,ab,kw OR 'knee':ti,ab,kw OR 'knees':ti,ab,kw

	3. [mh "immobilization"] OR 'immobilization':ti,ab,kw OR 'immobilisation':ti,ab,kw OR (restrict*):ti,ab,kw OR (stabiliz*):ti,ab,kw OR (stabilis*):ti,ab,kw 4. 1-3 AND **MEDLINE** (via PubMed interface) for systematic reviews or experimental studies using the following search strategy: 1. "Cervical Vertebrae/injuries"[Mesh] OR cervical injur*[TIAB] OR cervical spine*[TIAB] OR "Spinal Cord Injuries"[Mesh] OR spinal injur*[TIAB] OR spine injur*[TIAB] 2. "hand"[TIAB] OR "hands"[TIAB] OR "knee"[TIAB] OR "knees"[TIAB] OR "manual"[TIAB] 3. "Immobilization"[Mesh] OR immobiliz* [TIAB] OR immobilis* [TIAB] OR restrict* [TIAB] or stabiliz*[TIAB] or stabilis*[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) for systematic reviews or experimental studies using the following search strategy: 1. 'spinal cord injury'/exp OR 'cervical spine'/exp OR (cervical NEXT/1 injur*):ab:ti OR (cervical NEXT/1 spin*):ab:ti OR 'spine injury'/exp OR (spinal NEXT/1 injur*):ab:ti OR (spine NEXT/1 injur*):ab:ti 2. 'hand':ab:ti OR 'hands':ab:ti OR 'knee':ab:ti OR 'knees':ab:ti OR 'manual':ab:ti 3. 'fracture immobilization'/exp OR immobiliz*:ab:ti OR immobilis*:ab:ti OR restrict*:ab:ti OR 'spine stabilization'/exp OR stabiliz*:ab:ti OR stabilis*:ab:ti 1. 4. 1-3 AND
Search date	10 March 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies. **Language**: Include: English **Publication year**: Include: all years **Additional topic-related eligibility criteria:** **Population:** Excluded: intubated patients, patients undergoing endoscopic examination (e.g. bronchoscopy), patients undergoing the application of a cricoid 'yoke'

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No evidence was found using the above described search strategy and criteria.
Reference(s)	/

Whiplash – Correct placement of headrest (Prevention)

Question (PICO)	In humans (P), is correct placement of a headrest on the seat of a car (I) compared to no correct placement of the headrest (C) more effective to prevent a whiplash (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Neck injuries"] OR "neck injury":ti,ab OR "neck injuries":ti,ab OR whiplash*:ti,ab 2. (head NEXT restraint*):ti,ab 3. 1 AND 2 **MEDLINE** (via PubMed interface) using the following search strategy: 1. "neck injuries"[Mesh] OR "neck injury"[TIAB] OR "neck injuries"[TIAB] OR whiplash*[TIAB] 2. head restraint*[TIAB] 3. 1 AND 2 **Embase** (via Embase.com interface) using the following search strategy: 1. 'neck injury'/exp OR 'neck injury':ab,ti OR 'neck injuries':ab,ti OR whiplash*:ab,ti 2. (head NEXT/1 restraint*):ab,ti Articles retrieved with the above searches were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	19 August 2015
In/Exclusion criteria	**Population**: Include: adults and children **Intervention**: Include: specific/adapted placement of head restraint in car (vs no specific placement); Exclude: head restraint vs no head restraint **Outcome**: Include: whiplash, neck injury, neck pain; Exclude: studies with only whiplash patients and no control group without injury **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: conference abstracts, case series, cross-sectional studies (studies collecting information concerning type of car and injury in health insurance companies), animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline)

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Chapline, 2000, USA	Observational: case-control study	585 drivers of cars that were struck in the rear by another passenger vehicle.	Adequately positioned head restraint vs poorly positioned	Drivers were interviewed by telephone to determine demographics, extent and nature of the injuries and medical treatment received because of the crash. Vertical and horizontal distances from the driver's head to the head restraint were made using a straightedge ruler fitted with a bubble level. The driver was instructed to sit in the vehicle on level ground in a normal driving position with the head restraint in the same position as at the time of the crash.
Viano, 2001, Sweden	Observational: case-control study	People involved in single-event, rear-end crashes. The vehicles included the Saab 9000/900 equipped with a conventional seat and head restraint (n=85, 49±14y, 78±18 kg, 177±10 cm) and the Saab 9-5/9-3, which included the Self-Aligning Head Restraint (SAHR) (n=92, 45±14y, 79±16kg, 176±9cm) and modified seatback as standard equipment in front seats.	SAHR versus conventional seat and head restraint. The active head restraint, called SAHR (initially called the Self-Aligning Head Restraint and later the Saab Active Head Restraint) uses the momentum of the occupant pressing into the seatback in a rear crash to raise and move the head restraint forward providing earlier head-neck support and lowering loads causing neck extension.	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Neck pain	Adequately positioned head restraint vs poorly positioned	Women: Statistically significant: 32/109 vs 110/210 § RR: 0.56, 95%CI [0.41;0.77] (p=0.0004)* *In favour of adequately positioned head restraint*	1, 137 vs 448	Chapline, 2000

		Men: Not statistically significant: 5/28 vs 70/238 § RR: 0.61, 95%CI [0.27;1.38] ¥ (p=0.23)*		
Medium (≤10 weeks) to long-term (>10 weeks) whiplash injury	SAHR versus conventional seat and head restraint	Statistically significant: 4/92 vs 15/85 § RR: 0.25, 95%CI [0.09;0.71] (p=0.01)* *In favour of SAHR*	1, 92 vs 85	Viano, 2001

* The effect size was calculated by the reviewer(s) using the Review Manager Software
§ Imprecision (low number of events)
¥ Imprecision (large variability of results)

Quality of evidence

Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations
Chapline, 2000	Unclear (no demographic information comparing patients with and without neck pain)	No	Yes, no mention about confounders, however a sub-analysis for men and women was made	No	No
Viano, 2001	No	Yes, medium- (≤10 weeks) and long-term (>10 weeks) whiplash injuries were taken together as an outcome	Yes, not controlled for confounders such as gender	No	No

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Low number of events and large variability of results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Very Low [D]**	

Conclusion	There is limited evidence in favour of an adequately positioned head restraint Self-Aligning Head Restraint (SAHR) (Chapline 2000, Viano 2001). It was shown that SAHR resulted in a statistically significant reduction in medium- to long-term whiplash injuries, compared to a conventional seat and head restraint (Viano 2001). It was shown that an adequately positioned head restraint resulted in statistically significant decreased neck pain in women, compared to a poorly positioned head restraint. However, for men this could not be demonstrated (Chapline 2000). Evidence is of very low quality and results cannot be considered precise due to a low number of events and large variability of results.
Reference(s)	**Articles** Chapline JF, Ferguson SA, Lillis RP, Lund AK, Williams AF. *Neck pain and head restraint position relative to the driver's head in rear-end collisions*. Accid Anal Prev 2000, 32(2):287-97

	Viano DC, Olsen S. *The effectiveness of active head restraint in preventing whiplash.* J.Trauma 2001, 51(5):959-969

Stroke – Body position (First Aid)

Question (PICO)	Among persons with acute stroke (P), does a certain posture (I) compared to another posture (C) change functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health-related outcomes (O)?
Search Strategy	Databases **The Cochrane Library** using the following search strategy: 1. MeSH descriptor: [meta-analysis] explode all trees OR meta analys*:ti,ab,kw OR meta-analys*:ti,ab,kw OR 'cochrane':ti,ab,kw OR 'embase':ti,ab,kw OR 'pubmed':ti,ab,kw OR 'medline':ti,ab,kw OR 'reference list':ti,ab,kw OR 'reference lists':ti,ab,kw OR 'bibliography':ti,ab,kw OR 'bibliographies':ti,ab,kw OR 'hand-search':ti,ab,kw OR 'manual search':ti,ab,kw OR 'selection criteria':ti,ab,kw OR 'relevant journals':ti,ab,kw 2. MeSH descriptor: [stroke] explode all trees OR 'stroke':ti,ab,kw OR 'cerebrovascular accident':ti,ab,kw OR 'cva':ti,ab,kw 3. Mesh descriptor: [posture] explode all trees OR 'posture':ti,ab,kw OR 'postures':ti,ab,kw 4. Filter on date: from 2008 until 2015 (published NICE guideline in 2008) 5. Systematic reviews: 1-3 AND 6. Individual studies: 2-4 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti 2. 'Cerebrovascular accident'/exp OR 'stroke':ab,ti OR 'cerebrovascular accident':ab,ti OR cva:ab,ti 3. 'body posture'/exp OR posture:ab,ti OR postures:ab,ti 4. Filter on date: from 2008 until 2015 (published NICE guideline in 2008) 5. Systematic reviews: 1-3 AND 6. Individual studies: 2-4 AND **MEDLINE** (via PubMed interface) using the following search strategy: 1. Guideline [Publication Type] OR "Practice Guidelines as Topic"[Mesh] OR "Practice Guideline "[Publication Type] OR practice guideline*[TIAB] OR Meta-Analysis as Topic[Mesh] OR meta analy*[TIAB] OR metaanaly*[TIAB] OR Meta-Analysis[Publication Type] OR systematic review*[TIAB] OR systematic overview*[TIAB] OR Review Literature as Topic[Mesh] OR cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB] OR reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB] OR selection criteria[TIAB] OR data extraction[TIAB] 2. Stroke[mesh] OR stroke[tiab] OR "cerebrovascular accident"[tiab] OR cva[tiab] 3. Posture[Mesh] OR postures[tiab] OR posture[tiab] 4. Filter on date: from 2008 until 2015 (published NICE guideline in 2008) 5. Systematic reviews: 1-3 AND 6. Individual studies: 2-4 AND

	Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	09 March 2015
In/Exclusion criteria	**Population:** Include: patients with an acute stroke (ischemic/haemorrhagic) Exclude: we excluded studies on patients with stroke in a non-acute setting. **Intervention:** Include: any body position that can be provided by lay people. Exclude: any body position that cannot be provided by lay people (e.g. Trendelenburg position). **Comparison:** Include: studies that compare different body positions **Outcome:** Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Study design:** Include: a systematic review (of diagnostic accuracy studies) was included if the search strategy and selection criteria are clearly described and if at least MEDLINE and one other relevant database was searched. If no systematic review was published within the last 5 years, a search for individual experimental/observational studies was performed (from 2008-2015). Exclude: case series**,** cross-sectional studies, animal studies, *ex vivo* or *in vitro* studies. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year:** All years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Chatterton, 2000, United Kingdom	Experimental: Randomized controlled trial (within subjects design)	24 patients with acute stroke. Patients with previous or current condition which may predispose to hypoxic events or not for active treatment were excluded.	Intervention: - sitting up in bed (backrest @ 70°) - high side-lying (45°) on hemiplegic side - high side-lying (45°) on non-hemiplegic side Control: sitting in chair 1 hour in each position Position sequence was determined by a modified randomization procedure to avoid ordering effects and to ensure that the data collected corresponded to the first 60 minutes spent in the test position. If the patient was already in the test position, or one closely approximating it, this position was excluded from the randomization process at that stage.	Patients were tested in the following positions within 72 hours Sample size calculation was performed (a minimum of 12 patients would be needed to complete each position to have an 88% power to detect a difference of 2% in oxygen saturation.)
Elisabeth, 1993, United Kingdom	Experimental: Non-Randomized	10 patients with acute stroke. Patients with previous stroke,	Intervention: - right side dependent lying - left side dependent lying	Patients were tested in the following positions within 48 hours.

	trial (within subjects design)	irregular breathing, previous respiratory disease or cardiac failure were excluded.	- propped in bed (45°) Control: supine 30 minutes - 1 hour in each position The order of positions was in set order (non-randomized).	
Hunter, 2011, Australia	Experimental: Non-Randomized trial (within subjects design)	4 patients with an acute ischaemic stroke event. Patients with haemorrhagic stroke, complete recanalization (full reopening of the affected artery and restoration of normal blood flow velocity) at 24 hours, life-threatening comorbidities or unable to be flat in bed were excluded.	Intervention: - head of bed elevated at 30° - head of bed elevated at 15° Control: supine (head of bed elevated at 0°) 5 minutes in each position (1 minute of data recording) The order of positions was in set order (non-randomized).	Patients were tested within 24 hours The head frame was fitted and all measurements were obtained by the same experienced neurosonographer to maintain consistency throughout the procedure. Both assessors were unaware of participants' identification, diagnosis, and CT images to ensure unbiased and accurate interpretation of waveforms.
Rowat, 2001, United Kingdom	Experimental: Randomized controlled trial (within subjects design)	65 patients with acute stroke (within 7 days, median time = 72 hours) who were able to sit in a chair Patients with subarachnoid haemorrhage, uncooperative, able to walk or change position unaided were excluded.	Intervention: - sitting propped up in bed - side-lying on hemiplegic side - side-lying on non-hemiplegic side - supine Control: sitting in chair 10 minutes in each position The order was determined by random allocation generated by the computer. However, random allocation of the positions was not always possible, for example if the patient refused or was unable to get into that particular position, then the order of the positions had to be modified accordingly.	Power calculations were performed to ensure that the study included a sufficient number of stroke patients to detect the smallest clinically important difference in SaO2

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Body position versus sitting in chair				
Mean arterial oxygen saturation (%)	sitting up in bed (backrest @ 70°) versus sitting in chair	Not statistically significant: 95.76±2.19 vs 96.39±1.42 £ (p>0.05)	1,13 vs 12 (within subjects design)	Chatterton, 2000
	high side-lying (45°) on right side versus sitting in chair	Not statistically significant: 96.33±1.74 vs 96.39±1.42 £ (p>0.05)	1,17 vs 12 (within subjects design)	
		Statistically significant: 95.7±1.6 vs 96.0±1.6 £ (p<0.05) *In favour of sitting in chair*	1,65 vs 65 (within subjects design)	Rowat, 2001
	high side-lying (45°) on left side versus sitting in chair	Not statistically significant: 96.54±1.69 vs 96.39±1.42 £ (p>0.05)	1,14 vs 12 (within subjects design)	Chatterton, 2000
		Statistically significant: 95.0±2.4 vs 96.0±1.6 £ (p<0.05) *In favour of sitting in chair*	1, 65 vs 65 (within subjects design)	Rowat, 2001
	Sitting propped up in bed versus sitting in chair	Statistically significant: 95.6±1.6 vs 96.0±1.6 £ (p<0.05) *In favour of sitting in chair*	1, 63 vs 65 (within subjects design)	
	Supine versus sitting in chair	Not statistically significant: 95.7±1.6 vs 96.0±1.6 £ (p>0.05)	1, 62 vs 65 (within subjects design)	Rowat, 2001
	Lying on the paretic side versus sitting in chair	Statistically significant: 95.4±2.4 vs 96.0±1.6 £ (p<0.05) *In favour of sitting in chair*	1, 65 vs 65 (within subjects design)	
	Lying on the non-paretic side versus sitting in chair	Statistically significant: 95.3±2.4 vs 96.0±1.6 £ (p<0.05) *In favour of sitting in chair*	1, 65 vs 65 (within subjects design)	Rowat, 2001
Body position versus supine position				
Cerebral blood flow velocity for stroke-affected middle cerebral arteries (cm/sec)	Head of bed at 30° versus head of bed at 0° (supine)	Statistically significant: 51.5 (median) [44.25, interquartile range] vs 85 (median) [38.75, interquartile range] £ (p<0.05) *In favour of supine*	1, 4 vs 4 (within subjects design) §	Hunter, 2011
	Head of bed at 15° versus head of bed at 0° (supine)	Statistically significant: 55.5 (median) [56.5, interquartile range] vs 85 (median) [38.75, interquartile range] £ (p<0.05) *In favour of supine*		
Mean arterial oxygen saturation (%)	Lying on the paretic side versus supine	Not statistically significant: 89.4±4.3 vs 89.6±4.7 £ (p>0.05)	1, 10 vs 10 (within subjects design) §	Elisabeth, 1993
	Lying on the non-paretic side versus supine	Not statistically significant: 89.7±5.0 vs 89.6±4.7 £ (p>0.05)		
	Propped up in bed versus supine	Not statistically significant: 90.9±3.6 vs 94.0±1.5 £ (p>0.05)		

Mean ± SD (unless otherwise indicated)
§ Imprecision (limited sample size)
£ No effect size/CI available

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Chatterton, 2000	No	Yes	No	No	Within subjects design
Elisabeth, 1993	Yes (no randomization)	Yes	No	No	
Hunter, 2011	Yes (no randomization)	No	No	No	
Rowat, 2001	Yes/No	Yes	No	No	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	0	
Inconsistency	0	
Indirectness	-1	Indirect population (no stroke patients in first minutes/hours after stroke event), indirect outcomes (no patient-important outcomes such as morbidity, mortality, symptoms, quality of life)
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	<u>Sitting up in bed/Supine position versus sitting in a chair</u> There is limited evidence neither in favour of sitting up in bed/supine position nor sitting up in a chair. A statistical significant difference in mean arterial oxygen saturation between sitting up in bed/supine position and sitting in a chair could not be demonstrated. Evidence is of low quality. <u>Sitting propped in bed/lying on the (non-) paretic side versus sitting in a chair</u> There is limited evidence in favour of sitting in a chair. It was shown that the mean arterial oxygen saturation was statistically significant higher when sitting in a chair compared to sitting propped in bed/lying on the (non-) paretic side. However this statistical significant difference of about 1% (oxygen saturation) was considered as not clinically relevant. Evidence is of low quality. <u>Sitting propped in bed/lying on the (non-) paretic side versus supine position</u> There is limited evidence neither in favour of sitting propped in bed, lying on the (non-) paretic side nor the supine position. A statistical significant difference in mean arterial oxygen saturation between sitting propped in bed/lying on the (non-) paretic side and the supine position could not be demonstrated. Evidence is of low quality. <u>Supine position with head at 15°/30° versus supine position (with head at 0°)</u> There is limited evidence in favour of the supine position (with head at 0°). It was shown that the cerebral blood flow velocity for stroke-affected middle cerebral arteries was statistically significant higher in the supine position with the head at 0° compared to the supine position with the head at 15°/30°. Evidence is of low quality.
Reference(s)	**<u>Articles</u>**

	Chatterton HJ, Pomeroy VM, Connolly MJ, Faragher EB, Clayton L, Tallis RC. *The effect of body position on arterial oxygen saturation in acute stroke*. J Gerontol A Biol Sci Med Sci. 2000,55:239-244 Elizabeth J, Singarayar J, Ellul J, Barer D, Lye M. *Arterial oxygen saturation and posture in acute stroke.* Age Ageing 1993,22:269-272 Hunter AJ, Snodgrass SJ, Quain D, Parsons MW, Levi CR. *HOBOE (Head-of-Bed Optimization of Elevation) Study: association of higher angle with reduced cerebral blood flow velocity in acute ischemic stroke.* Phys Ther 2011,91:1503-1512 Rowat AM, Wardlaw JM, Dennis MS, Warlow CP. *Patient positioning influences oxygen saturation in the acute phase of stroke*. Cerebrovasc Dis. 2001;12:66-72.

Epilepsy – Posture (First Aid)

Question (PICO)	Among persons with epileptic seizures (P), does a certain posture (I) compared to another posture (C) change functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Seizures"] OR [mh "Epilepsy"] OR (convulsion*):ti,ab,kw OR (fits):ti,ab,kw 2. [mh "Posture"] OR (Posture):ti,ab,kw OR (Position):ti,ab,kw 3. 1 AND 2 **MEDLINE** (via PubMed interface) using the following search strategy: 1. "seizures" [Mesh] OR "epilepsy" [Mesh] OR seizure*[TIAB] OR epilep*[TIAB] OR convulsion*[TIAB] OR fits[TIAB] 2. "Posture"[Mesh] OR position*[TIAB] OR posture[TIAB] OR restrain*[TIAB OR restrict*[TIAB] 3. "First Aid"[Mesh] OR "Community Health Workers"[Mesh] OR "Emergency Treatment"[Mesh:NoExp] OR "Emergency Medical Services"[Mesh:NoExp] OR "Emergency Service, Hospital"[Mesh] OR "Poison Control Centers"[Mesh] OR "Transportation of Patients"[Mesh] OR "Primary Health Care"[Mesh:NoExp] OR "Acute disease"[Mesh] OR "emergencies" [Mesh] OR "self care"[Mesh] OR "acute management" [TIAB] OR "immediate care" [TIAB] OR "prehospital treatment" [TIAB] OR "first aid" TIAB] OR "self care"[TIAB] OR emergenc*[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) for systematic reviews or experimental studies using the following search strategy: 1. 'seizure, epilepsy and convulsion'/exp OR epilep*:ab:ti OR seizure*:ab:ti OR convulsion*:ab:ti OR 'fits':ab:ti 2. 'body position'/exp OR position*:ab:ti OR 'posture':ab:ti OR restrain*:ab:ti OR restrict*:ab:ti 3. 'first aid'/exp OR 'health auxiliary'/exp OR 'emergency treatment'/de OR 'emergency health service'/exp OR 'poison center'/exp OR 'patient transport'/exp OR 'primary health care'/exp OR 'acute disease'/exp OR 'emergency'/exp OR 'self care'/exp OR 'acute management':ab,ti OR 'immediate care':ab,ti OR 'prehospital treatment':ab,ti OR 'self care':ab,ti OR 'first aid':ab,ti OR emergenc*:ab,ti
Search date	03 March 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms.

	Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies. **Language**: Include: English **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Epilepsy – Object in mouth (First Aid)

Question (PICO)	Among persons with epileptic seizures (P), does putting an object in the mouth (I) compared to doing nothing (C) change pain and complications (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the search terms: 1. [mh "Seizures"] OR [mh "Epilepsy"] OR (convulsion*):ti,ab,kw OR (fits):ti,ab,kw 2. mouth:ti,ab,kw AND ((object*):ti,ab,kw OR wallet:ti,ab,kw OR spoon:ti,ab,kw) 3. 1 AND 2 **MEDLINE** (via PubMed interface) using the following search strategy: 1. "seizures" [Mesh] OR "epilepsy" [Mesh] OR seizure*[TIAB] OR epilep*[TIAB] OR convulsion*[TIAB] OR fits[TIAB] 2. (wallet[TIAB] OR spoon[TIAB] OR bite[TIAB] OR object*[TIAB]) AND mouth[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) for systematic reviews or experimental studies using the following search strategy: 1. 'seizure, epilepsy and convulsion'/exp OR epilep*:ab,ti OR seizure*:ab,ti OR convulsion*:ab,ti OR 'fits':ab,ti 2. ('wallet':ab,ti OR 'spoon':ab,ti OR 'bite':ab,ti OR object*:ab,ti) AND 'mouth':ab,ti 3. 1-2 AND
Search date	02 March 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages.

	Intervention: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies. **Language**: Include: English **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Eye injury – Covering both eyes (First Aid)

Question (PICO)	Among persons with an eye injury (P), does covering both eyes (I) compared to not covering both eyes (C) change functional recovery, pain, complications, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the search terms: 1. [mh "Eye Injuries"] OR ((eye*):ti,ab,kw AND (injur*):ti,ab,kw)) 2. (Patch) :ti,ab,kw OR (pad) :ti,ab,kw OR (cover) :ti,ab,kw 3. 1 AND 2 **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Eye injuries" [Mesh] OR eye*[TIAB] AND injur*[TIAB] 2. patch[TIAB] OR patching[TIAB] OR patched[TIAB] OR pad[TIAB] OR padding[TIAB] OR padded[TIAB] OR cover[TIAB] OR covering[TIAB] OR covered[TIAB] 3. 1 AND 2 **Embase** (via Embase.com interface) using the following search strategy:

	1. 'eye injury'/exp OR (eye*:ab,ti AND injur*:ab,ti) 2. patch*:ab,ti OR pad*:ab,ti OR cover*:ab,ti 3. 1 AND 2
Search date	2 August 2012
In/Exclusion criteria	**Population**: Include: People with eye injury. **Intervention**: Include: Covering of both eyes without pressure. Exclude: Covering of only one eye, pressure applied during covering, use of antibiotic ointment. **Outcome**: Include: functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion(s)	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Eye injury – Removal of speck (First Aid)

Question (PICO)	In humans with a speck in the eye (P), is removing the speck with a tissue or a cotton swab (I) compared to irrigating the eye with water (C) effective to remove the speck (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "eye foreign bodies"] OR "eye injury":ti,ab OR "eye injuries":ti,ab **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Eye Foreign Bodies"[Mesh] 2. "Eye Injuries"[Mesh] OR "eye injury"[TIAB] OR "eye injuries"[TIAB] 3. "Foreign Bodies"[Mesh] OR foreign bod*[TIAB] OR speck[TIAB] OR object[TIAB] 4. 2 AND 3 5. 1 OR 4 6. "cotton bud"[TIAB] OR "cotton swab"[TIAB] OR "q tip"[TIAB] OR removal[TIAB] OR remove[TIAB]

	7. 5 AND 6 **Embase** (via Embase.com interface) using the following search strategy: 1. 'intraocular foreign body'/exp 2. 'eye injury'/exp OR 'eye injury':ab,ti OR 'eye injuries':ab,ti 3. 'foreign body'/exp OR (foreign NEXT/1 bod*):ab,ti OR speck:ab,ti OR object:ab,ti 4. 2 AND 3 5. 1 OR 4 6. 'cotton bud':ab,ti OR 'cotton swab':ab,ti OR 'q tip':ab,ti OR removal:ab,ti OR remove:ab,ti 7. 5 AND 6
Search date	21 August 2015
In/Exclusion criteria	**Population**: Include: humans with a speck or foreign body in the eye **Intervention**: Include: removal of the object with a tissue or cotton swab (compared to irrigation of the eye) **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion(s)	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Eye injury – Temperature rinsing fluid (First Aid)

Question (PICO)	In humans with eye injury (I), is rinsing the eye with room temperature fluids (I) compared to rinsing the eye with warm or cold fluids (C) effective to change functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms (O)?
Search Strategy	Databases

	The Cochrane Library (systematic reviews and controlled trials) using the following search strategy: 1. [mh Eye] OR eye*:ti,ab,kw OR ocular:ti,ab,kw 2. cleans*:ti,ab,kw OR irrigat*:ti,ab,kw 3. [mh temperature] OR warm:ti,ab,kw OR temperature*:ti,ab,kw 4. 1-3 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. eye[Mesh] OR eye*[TIAB] OR ocular[TIAB] 2. cleans*[TIAB] OR irrigat*[TIAB] 3. temperature[Mesh] OR warm*[TIAB] OR temperature*[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Eye/exp OR eye*:ab,ti OR ocular:ab,ti 2. Cleans*:ab,ti OR irrigat*¨:ab,ti 3. 'water temperature'/exp OR Warm:ab,ti OR temperature:ab,ti 4. 1-3 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	17 August 2015
In/Exclusion criteria	**Population**: People with eye injury or healthy volunteers **Intervention**: room temperature fluids **Comparison**: cold or warm fluids **Outcome**: discomfort, pain **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Ernst, 1998, USA	Experimental: Randomized controlled trial (within subjects design)	35 volunteers (20 women, 15 men), mean age 35±8 years, received warmed and room temperature saline solution ocular irrigation.	1. Room temperature saline solution: 21.1°C 2. Warm saline solution: 32.2°C-37.8°C	It was estimated it would require 33 pairs of eyes to provide 80% power to detect a difference of at least 12 mm in VAS readings.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
discomfort (100 mm VAS scale)	room temperature vs warm saline solution	Statistically significant: 34±24 vs 15±15 MD: 19, 95%CI [10; 28] p<0.001 *In favour of warm saline solution*	1, 35 vs 35 (within subjects design)	Ernst, 1998

Mean ± SD (unless otherwise indicated)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Ernst, 1998	No, order of eyes and solutions were randomized	Yes, subjects perceived temperature differences. Investigators were blinded.	No	No	Within subjects design

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	0	
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading High [A]**	

Conclusion	There is evidence in favour of warm saline solution. It was shown that warm saline solution resulted in a statistically significant decrease of discomfort, compared to saline solution at room temperature (Ernst 1998). Evidence is of high quality.
Reference(s)	**Individual studies** Ernst AA, Thomson T, Haynes M, Weiss SJ. *Warmed versus room temperature saline solution for ocular irrigation: a randomized clinical trial*. Annals of Emergency Medicin 1998, 32(6): 676-679

Eye injury – Eye protection (Prevention)

Question (PICO)	In humans (P), is wearing eye protection (I) compared to not doing this (C) effective to prevent eye injuries (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "eye injuries"] OR eye injur*:ti,ab,kw 2. [mh "eye protective devices"] OR (eye:ti,ab,kw AND protect*":ti,ab,kw) 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "eye injuries"[Mesh] OR eye injur*[TIAB] 2. "eye protective devices"[Mesh] OR eye protect*[TIAB] 3. 1-2 AND

	Embase (via Embase.com interface) using the following search strategy: 1. 'eye injury'/exp OR (eye NEXT/1 injur*):ab,ti 2. 'eye protection'/exp OR (eye NEXT/1 protect*):ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	18 August 2015
In/Exclusion criteria	**Population**: Include: healthy people of all ages. **Intervention**: Include: eye protection. Exclude: Eye protection in medical professions or sports. Educational interventions. **Comparison**: Include: no eye protection **Outcome**: Include: eye injury **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Yu, 2004, China	Observational: case-control study	239 patients (mean age 39.3 years±11.3 years; 220 males, 19 females) with work-related eye injuries attending the ophthalmology clinics of 3 major public hospitals in Hong Kong during first 3 months of 2000. Controls were selected from general population based on the residential telephone directory of Hong Kong. Controls (n=251) (mean age 38.2±12.5 years; 232 males, 19 females) were matched to cases based on gender.	Safety glasses vs no safety glasses	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Eye injury	Safety glasses vs no safety glasses	Statistically significant: 27/44 vs 130/154 § OR: 0.29, 95%CI [0.14;0.62] (p=0.001)* *In favour of safety glasses*	1, 44 vs 154	Yu, 2004

* Calculations done by the reviewer(s) using Review Manager software

§ Imprecision (low number of events)

Quality of evidence

Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations
Yu, 2004	No, cases and controls were matched based on gender	No	No, different models were tested, taking into account several variables	No	hospital based design, possible self-selection bias

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Low number of events
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Conclusion	There is limited evidence in favour of safety glasses. It was shown that wearing safety glasses resulted in a statistically significant decrease of eye injuries, compared to not wearing safety glasses (Yu 2004). Evidence is of very low quality and results cannot be considered precise due to low number of events.
Reference(s)	**Individual studies** Yu TSI, Liu HL, Hui K. *A case-control study of eye injuries in the workplace in Hong Kong*. Ophtalmology 2004, 111:70-74

Eye injury – Sharp objects (Risk Factor)

Question (PICO)	In humans (P), is playing/working with sharp objects (RF) compared to not doing this (C) a risk factor for eye injuries (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "eye injuries"] OR eye injur*:ti,ab,kw) 2. [mh "risk factors"] OR "risk factor*":ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "eye injuries"[Mesh] OR eye injur*[TIAB] 2. "risk factors"[Mesh] OR "risk factor*"[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'eye injury'/exp OR (eye NEXT/1 injur*):ab,ti 2. 'risk factor'/exp OR (risk:ab,ti AND (factor:ab,ti OR factors:ab,ti)) 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).

Search date	17 August 2015
In/Exclusion criteria	**Population**: Include: Healthy people of all ages. **Intervention**: Include: sharp objects, chemical liquids, corrosive gases/vapours. **Outcome**: Include: eye injuries. **Study design:** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Risk factor	Remarks
Yu, 2004, China	Observational: case-control study	239 patients (mean age 39.3 years±11.3 years; 220 males, 19 females) with work-related eye injuries attending the ophthalmology clinics of 3 major public hospitals in Hong Kong during the first 3 months of 2000. Controls were selected from general population based on the residential telephone directory of Hong Kong. Controls (n=251) (mean age 38.2±12.5 years; 232 males, 19 females) were matched to cases based on gender.	Exposure to sharply pointed objects vs no sharply pointed objects	

Synthesis of findings

Outcome	Risk factor	Effect Size	#studies, # participants	Reference
Eye injury	Sharply pointed objects vs no sharply pointed objects	Statistically significant: 181/239 vs 58/253 § OR: 10.49, 95%CI [6.92; 15.91] (p<0.00001)* *With harm for exposure to sharply pointed objects*	1, 239 vs 253	Hu, 2004

* Calculations done by the reviewer(s) using Review Manager software

§ Imprecision (low number of events)

Quality of evidence

Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations
Yu, 2004	No, cases and controls were matched based on gender	No	No, different models were tested, taking into	No	hospital based design, possible self-selection bias

			account several variables		

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Low number of events
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Conclusion	There is limited evidence with harm for exposure to sharp pointed objects. It was shown that exposure to sharp pointed objects resulted in a statistically significant increased risk of eye injuries, compared to no exposure to sharp pointed objects (Yu 2004). Evidence is of very low quality and results cannot be considered precise due to low number of events.
Reference(s)	**Individual studies** Yu TSI, Liu HL, Hui K. *A case-control study of eye injuries in the workplace in Hong Kong*. Ophtalmology 2004, 111:70-74

Earache – Heat or cold application (First Aid)

Question (PICO)	In people with earache (I) is applying heat or cold (I) vs not doing this (C) effective to decrease earache (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "earache"] OR [mh "otitis"] OR earache:ti,ab,kw OR otalgia:ti,ab,kw 2. Hot:ti,ab,kw OR warm:ti,ab,kw OR heat:ti,ab,kw OR cold:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Earache[Mesh] OR otitis[Mesh] OR otalgia[TIAB] OR earache[TIAB] 2. Hot[TIAB] OR warm[TIAB] OR heat[TIAB] OR cold[TIAB] OR Ice[Mesh] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Otalgia/exp OR otitis/exp OR otalgia:ab,ti OR earache:ab,ti 2. Hot:ab,ti OR warm:ab,ti OR heat:ab,ti OR cold:ab,ti OR 'ice'/exp 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	2 March 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence).

	Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Earache – Paracetamol (First Aid)

Question (PICO)	In humans with earache (P) is taking paracetamol (I) compared to not taking paracetamol (C) effective to reduce the pain (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh Earache] or earache:ti,ab,kw or [mh otitis] or otitis:ti,ab,kw or otalgia:ti,ab,kw 2. [mh acetaminophen] OR paracetamol:ti,ab,kw OR acetaminophen:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Earache[Mesh] OR earache[TIAB] OR otitis[Mesh] OR otitis[TIAB] OR otalgia[TIAB] 2. Acetaminophen[Mesh] OR paracetamol[TIAB] OR acetaminophen[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'otalgia'/exp OR earache:ab,ti OR 'otitis media'/exp OR otitis:ab,ti OR otalgia:ab,ti

	2. Paracetamol/exp OR acetaminophen:ab,ti OR paracetamol:ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	13 August 2015
In/Exclusion criteria	**Population**: Include: adults and children with earache. **Intervention**: Include: paracetamol. Exclude: intravenous paracetamol or topical analgesia. **Comparison**: Include: placebo. Exclude: other analgesics such as ibuprofen. **Outcome**: Include: pain relief. **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Bertin, 1996, France	Experimental: randomized controlled trial	219 children (122 males, 97 females), mean age 2.98±1.33 years, with otoscopically proven acute otitis media (30 November 1988-3 March 1990).	1. Ibuprofen (n=71) 2. Acetaminophen (n=73) 3. Placebo (n=75) [Data on ibuprofen were not extracted]	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Otalgia	Acetaminophen vs placebo	Statistically significant: 7/73 vs 19/75 § OR: 0.31, 95%CI [0.12;0.80] (p=0.01)* *In favour of paracetamol*	1, 73 vs 75	Bertin, 1996

* Calculations done by the reviewer(s) using Review Manager software

§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Bertin, 1996	No, computer generated list	No, identical looking microgranules	No	No	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Low number of events
Inconsistency	0	
Indirectness	0	
Publication bias	-1	Conflict of interest: one of the authors works with the company who provided the treatments
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is limited evidence in favour of paracetamol. It was shown that paracetamol resulted in a statistically significant decrease of otalgia, compared to no paracetamol (Bertin 1996). Evidence is of low quality and results cannot be considered precise due to limited sample size.
Reference(s)	**Articles** Bertin L, d'Athis P, Duhamel JF, Maudelonde C, Lasfargues G, Guillot M, Marsac A, Debregeas B, Olive G. *A randomized, double-blind, multicenter controlled trial of ibuprofen versus acetaminophen and placebo for symptoms of acute otitis media in children*. Fundam Clin Pharmacol 1996, 10:387-392

Ear clearing – Toynbee technique (First Aid)

Question (PICO)	In humans with earache (P), is the Toynbee technique (I) compared to no intervention (C) effective to clear the ears (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh ear] OR ear:ti,ab,kw 2. Clear*:ti,ab,kw OR equaliz*:ti,ab,kw 3. [mh yawning] OR yawn*:ti,ab,kw OR [mh deglutition] OR swallow*:ti,ab,kw OR [mh "chewing gum"] OR chew*:ti,ab,kw OR [mh "Valsalva maneuver"] OR ((Toynbee:ti,ab,kw OR Valsalva:ti,ab,kw OR Frenzel:ti,ab,kw OR Lowry:ti,ab,kw OR Edmonds:ti,ab,kw) AND (maneuver:ti,ab,kw OR manoeuvre:ti,ab,kw OR technique:ti,ab,kw)) 4. 1-3 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Ear[Mesh] OR ear[TIAB] 2. Clear*[TIAB] OR equaliz*[TIAB] 3. Yawning[Mesh] OR Yawn*[TIAB] OR deglutition[Mesh] OR swallow*[TIAB] OR "chewing gum"[Mesh] OR chew*[TIAB] OR "Valsalva maneuver"[Mesh] OR ((Toynbee[TIAB] OR Valsalva[TIAB] OR Frenzel[TIAB] OR Lowry[TIAB] OR Edmonds[TIAB]) AND (maneuver[TIAB] OR manoeuvre[TIAB] OR technique[TIAB])) 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Ear/exp OR ear:ab,ti 2. Clear*:ab,ti OR equaliz*:ab,ti 3. Yawning/exp OR yawn*:ab,ti OR swallowing/exp OR swallow*:ab,ti OR 'chewing gum'/exp OR chew*:ab,ti OR 'valsalva maneuver'/exp OR ((Valsalva:ab,ti OR Toynbee:ab,ti OR Frenzel:ab,ti OR Lowry:ab,ti OR Edmonds:ab,ti) AND (maneuver:ab,ti OR manoeuvre:ab,ti OR technique:ab,ti))

	4. 1-3 AND
Search date	12 August 2015
In/Exclusion criteria	**Population**: Include: People with earache or healthy volunteers. Exclude: scuba divers. **Intervention**: Include: Toynbee technique **Comparison**: Include: no intervention **Outcome**: Include: clearing or equalization of the ears. **Study design:** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Ear clearing – Valsalva technique (First Aid)

Question (PICO)	In humans with earache (P), is the Valsalva technique (I) compared to no intervention (C) effective to clear the ears (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh ear] OR ear:ti,ab,kw 2. Clear*:ti,ab,kw OR equaliz*:ti,ab,kw 3. [mh yawning] OR yawn*:ti,ab,kw OR [mh deglutition] OR swallow*:ti,ab,kw OR [mh "chewing gum"] OR chew*:ti,ab,kw OR [mh "Valsalva maneuver"] OR ((Toynbee:ti,ab,kw OR Valsalva:ti,ab,kw OR Frenzel:ti,ab,kw OR Lowry:ti,ab,kw OR Edmonds:ti,ab,kw) AND (maneuver:ti,ab,kw OR manoeuvre:ti,ab,kw OR technique:ti,ab,kw)) 4. 1-3 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Ear[Mesh] OR ear[TIAB] 2. Clear*[TIAB] OR equaliz*[TIAB]

	3. Yawning[Mesh] OR Yawn*[TIAB] OR deglutition[Mesh] OR swallow*[TIAB] OR "chewing gum"[Mesh] OR chew*[TIAB] OR "Valsalva maneuver"[Mesh] OR ((Toynbee[TIAB] OR Valsalva[TIAB] OR Frenzel[TIAB] OR Lowry[TIAB] OR Edmonds[TIAB]) AND (maneuver[TIAB] OR manoeuvre[TIAB] OR technique[TIAB])) 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Ear/exp OR ear:ab,ti 2. Clear*:ab,ti OR equaliz*:ab,ti 3. Yawning/exp OR yawn*:ab,ti OR swallowing/exp OR swallow*:ab,ti OR 'chewing gum'/exp OR chew*:ab,ti OR 'valsalva maneuver'/exp OR ((Valsalva:ab,ti OR Toynbee:ab,ti OR Frenzel:ab,ti OR Lowry:ab,ti OR Edmonds:ab,ti) AND (maneuver:ab,ti OR manoeuvre:ab,ti OR technique:ab,ti)) 4. 1-3 AND
Search date	12 August 2015
In/Exclusion criteria	**Population**: Include: People with earache or healthy volunteers. Exclude: scuba divers. **Intervention**: Include: Valsalva technique **Comparison**: Include: no intervention **Outcome**: Include: clearing or equalization of the ears. **Study design:** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Ear clearing – Yawning, swallowing, chewing gum (First Aid)

Question (PICO)	In humans with earache (P), is swallowing, yawning or chewing gum (I) compared to not doing this (C) effective to clear the ears (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh ear] OR ear:ti,ab,kw

	2. Clear*:ti,ab,kw OR equaliz*:ti,ab,kw 3. [mh yawning] OR yawn*:ti,ab,kw OR [mh deglutition] OR swallow*:ti,ab,kw OR [mh "chewing gum"] OR chew*:ti,ab,kw OR [mh "Valsalva maneuver"] OR ((Toynbee:ti,ab,kw OR Valsalva:ti,ab,kw OR Frenzel:ti,ab,kw OR Lowry:ti,ab,kw OR Edmonds:ti,ab,kw) AND (maneuver:ti,ab,kw OR manoeuvre:ti,ab,kw OR technique:ti,ab,kw)) 4. 1-3 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Ear[Mesh] OR ear[TIAB] 2. Clear*[TIAB] OR equaliz*[TIAB] 3. Yawning[Mesh] OR Yawn*[TIAB] OR deglutition[Mesh] OR swallow*[TIAB] OR "chewing gum"[Mesh] OR chew*[TIAB] OR "Valsalva maneuver"[Mesh] OR ((Toynbee[TIAB] OR Valsalva[TIAB] OR Frenzel[TIAB] OR Lowry[TIAB] OR Edmonds[TIAB]) AND (maneuver[TIAB] OR manoeuvre[TIAB] OR technique[TIAB])) 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Ear/exp OR ear:ab,ti 2. Clear*:ab,ti OR equaliz*:ab,ti 3. Yawning/exp OR yawn*:ab,ti OR swallowing/exp OR swallow*:ab,ti OR 'chewing gum'/exp OR chew*:ab,ti OR 'valsalva maneuver'/exp OR ((Valsalva:ab,ti OR Toynbee:ab,ti OR Frenzel:ab,ti OR Lowry:ab,ti OR Edmonds:ab,ti) AND (maneuver:ab,ti OR manoeuvre:ab,ti OR technique:ab,ti)) 4. 1-3 AND
Search date	12 August 2015
In/Exclusion criteria	**Population**: Include: People with earache or healthy volunteers. Exclude: scuba divers. **Intervention**: Include: yawning, swallowing or chewing gum **Comparison**: Include: no intervention **Outcome**: Include: clearing or equalization of the ears. **Study design:** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Earache – lying down (Risk Factor)

Question (PICO)	In humans with earache (P) is lying down (RF) compared to not lying down (C) a risk factor for increased pain (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh Earache] OR earache:ti,ab,kw OR [mh otitis] OR otitis:ti,ab,kw OR otalgia:ti,ab,kw 2. [mh "supine position"] OR [mh "prone position"] OR supine:ti,ab,kw OR prone:ti,ab,kw OR horizontal:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Earache[Mesh] OR earache[TIAB] OR otitis[Mesh] OR otitis[TIAB] OR otalgia[TIAB] 2. "supine position"[Mesh] OR "prone position"[Mesh] OR supine[TIAB] OR prone[TIAB] OR horizontal[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Otalgia/exp OR earache:ab,ti OR 'otitis media'/exp OR otitis:ab,ti OR otalgia:ab,ti 2. 'supine position'/exp OR supine:ab,ti OR prone:ab,ti OR horizontal:ab,ti 3. 1-2 AND
Search date	12 August 2015
In/Exclusion criteria	**Population**: Include: patients with earache. **Intervention**: Include: lying down: supine or prone position, horizontal position. Exclude: other positions, vertical position, standing position. **Outcome**: Include: pain. **Study design:** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Foreign object in nose – Blowing the nose (First Aid)

Question (PICO)	In humans with a foreign object in the nose (I), is blowing the nose (I) compared to not blowing the nose (C) effective to remove the foreign object (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "foreign bodies"] OR "foreign body":ti,ab,kw OR "foreign bodies":ti,ab,kw 2. [mh "Nasal obstruction"] OR ((nasal:ti,ab,kw OR nose:ti,ab,kw) AND obstruction:ti,ab,kw) 3. 1-2 OR 4. Blow*:ti,ab,kw AND nose:ti,ab,kw 5. 3-4 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Foreign Bodies"[Mesh] OR "foreign body"[TIAB] OR "foreign bodies"[TIAB] 2. "Nasal obstruction"[Mesh] OR ((nasal[TIAB] OR nose[TIAB]) AND obstruction[TIAB]) 3. 1-2 OR 4. Blow*[TIAB] AND nose[TIAB] 5. 3-4 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'foreign body'/exp OR 'foreign body':ab,ti OR 'foreign bodies':ab,ti 2. 'nose obstruction'/exp OR ((nasal:ab,ti OR nose:ab,ti) AND obstruction:ab,ti) 3. 1-2 OR 4. Blow*:ab,ti AND nose*:ab,ti 5. 3-4 AND
Search date	17 August 2015
In/Exclusion criteria	**Population**: Include: children with a foreign object in their nose **Intervention**: Include: blowing the nose **Comparison**: Include: not blowing the nose **Outcome**: Include: Removal of the object **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Foreign object in nose – Parent's kiss (First Aid)

Question (PICO)	In humans with a foreign object in the nose (I), is the blow-kiss method (I) compared to doing nothing (C) effective to remove the foreign object (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "foreign bodies"] OR "foreign body":ti,ab,kw OR "foreign bodies":ti,ab,kw 2. [mh "Nasal obstruction"] OR ((nasal:ti,ab,kw OR nose:ti,ab,kw) AND obstruction:ti,ab,kw) 3. 1-2 OR 4. (Parent*:ti,ab,kw OR mother*:ti,ab,kw) AND kiss:ti,ab,kw 5. 3-4 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Foreign Bodies"[Mesh] OR "foreign body"[TIAB] OR "foreign bodies"[TIAB] 2. "Nasal obstruction"[Mesh] OR ((nasal[TIAB] OR nose[TIAB]) AND obstruction[TIAB]) 3. 1-2 OR 4. (Parent*[TIAB] OR mother*[TIAB]) AND kiss[TIAB] 5. 3-4 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'foreign body'/exp OR 'foreign body':ab,ti OR 'foreign bodies':ab,ti 2. 'nose obstruction'/exp OR ((nasal:ab,ti OR nose:ab,ti) AND obstruction:ab,ti) 3. 1-2 OR 4. (Parent*:ab,ti OR mother*:ab,ti) AND kiss:ab,ti 5. 3-4 AND
Search date	17 August 2015
In/Exclusion criteria	**Population**: Include: children with a foreign object in their nose **Intervention**: Include: parent's kiss (=mother's kiss). Exclude: other ways to remove the object (e.g. surgical) **Comparison**: Include: not removing the object **Outcome**: Include: Successful removal of the object **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Toothache – Heat application (First Aid)

Question (PICO)	In people who are suffering from toothache (P) is heat application (I) vs not doing this (C) effective to decrease symptoms of pain (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "toothache"] OR toothache:ti,ab,kw OR (tooth NEXT pain):ti,ab,kw 2. heat:ti,ab,kw OR hot:ti,ab,kw OR warm:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for systematic reviews, experimental and observational studies using the following search strategy: 1. "toothache"[TIAB] OR "tooth pain"[TIAB] OR "toothache"[Mesh] 2. "heat"[TIAB] OR "hot"[TIAB] OR "warm"[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) for systematic reviews, experimental and observational studies using the following search strategy: 1. 1.'tooth pain'/exp OR 'toothache':ab,ti OR 'tooth pain':ab,ti 2. 'heat':ab,ti OR 'hot':ab,ti OR 'warm':ab,ti 3. 1-2 AND
Search date	24 February 2015
In/Exclusion criteria	**General project-related eligibility criteria:** **Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched.

	An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies. **Topic-related study eligibility criteria:** **Intervention:** included: gargling with or drinking hot beverage **Outcome**: excluded: inflamed or infected socke, alveolar osteitis

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No evidence was found using the above described search strategy and criteria.
Reference(s)	/

Toothache – Cold application (First Aid)

Question (PICO)	In people who are suffering from toothache (P) is cold application (I) vs not doing this (C) effective to decrease symptoms of pain (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "toothache"] OR toothache:ti,ab,kw OR (tooth NEXT pain):ti,ab,kw 2. [mh"ice"] OR ice:ti,ab,kw OR cold:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for systematic reviews, experimental and observational studies using the following search strategy: 1. "toothache"[TIAB] OR "tooth pain"[TIAB] OR "toothache"[Mesh] 2. cold[TIAB] OR ice[Mesh] OR ice[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) for systematic reviews, experimental and observational studies using the following search strategy: 1. 'tooth pain'/exp OR 'toothache':ab:ti OR 'tooth pain':ab:ti 2. cold:ab,ti OR 'ice'/exp OR ice:ab,ti 3. 1-2 AND
Search date	08 February 2016
In/Exclusion criteria	**Population**: Include: people with toothache. **Intervention**: Include: cold/ice application. Exclude: heath application. **Outcome**: Include: pain. Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched.

	An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Toothache – Paracetamol (First Aid)

Question (PICO)	In humans with toothache (P) is taking paracetamol (I) compared to not taking paracetamol (C) effective to reduce the pain (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh Tootache] or toothache:ti,ab,kw OR ((tooth:ti,ab,kw OR dental:ti,ab,kw) AND (ache:ti,ab,kw OR pain:ti,ab,kw)) OR odontalgia:ti,ab,kw 2. [mh acetaminophen] OR paracetamol:ti,ab,kw OR acetaminophen:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Toothache[Mesh] OR toothache[TIAB] OR ((tooth[TIAB] OR dental[TIAB]) AND (ache[TIAB] OR pain[TIAB])) OR odontalgia[TIAB] 2. Acetaminophen[Mesh] OR paracetamol[TIAB] OR acetaminophen[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'tooth pain'/exp OR toothache:ab,ti OR ((tooth:ab,ti OR dental:ab,ti) AND (ache:ab,ti OR pain:ab,ti)) OR odontalgia:ab,ti 2. Paracetamol/exp OR acetaminophen:ab,ti OR paracetamol:ab,ti 3. 1-2 AND
Search date	13 August 2015
In/Exclusion criteria	**Population**: Include: adults and children with toothache. Exclude: people with postoperative tooth pain. **Intervention**: Include: paracetamol. Exclude: combinations of paracetamol with codeine, intravenous paracetamol or topical analgesia. **Comparison**: Include: placebo. Exclude: other analgesics such as ibuprofen.

	Outcome: Include: pain relief. **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Sore throat – Drinking (First Aid)

Question (PICO)	In people with a sore throat (P), is drinking (I) vs not drinking (C) effective to decrease symptoms of pain (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh pharyngitis] OR throat*:ti,ab,kw OR pharyngitis:ti,ab,kw 2. [mh drinking] OR drink*:ti,ab,kw OR consumption:ti,ab,kw OR ingestion:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Pharyngitis[Mesh] OR throat*[TIAB] OR pharyngitis[TIAB] 2. Drinking[Mesh] OR ((fluid[TIAB] OR liquid[TIAB]) AND (consumption[TIAB] OR ingestion[TIAB])) OR drink*[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'sore throat'/exp OR 'pharyngitis'/exp OR throat*:ab,ti OR pharyngitis:ab,ti 2. 'drinking'/exp OR ((fluid:ab,ti OR liquid:ab,ti) AND (consumption:ab,ti OR ingestion:ab,ti)) OR drink*:ab,ti 3. 1-2 AND
Search date	6 March 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages.

	Intervention: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Sore throat – Paracetamol (First Aid)

Question (PICO)	In people with a sore throat (P), is taking paracetamol (I) vs not doing this (C) effective to decrease symptoms of pain (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh pharyngitis] OR throat*:ti,ab,kw OR pharyngitis:ti,ab,kw 2. [mh acetaminophen] OR [mh analgesics] OR paracetamol:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Pharyngitis[Mesh] OR throat*[TIAB] OR pharyngitis[TIAB]

	2. "Acetaminophen"[Mesh] OR analgesics[Mesh] OR Paracetamol[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'sore throat'/exp OR throat*:ab,ti OR pharyngitis:ab,ti 2. 'paracetamol'/exp OR paracetamol:ab,ti 3. 1-2 AND Guidelines, systematic reviews, retrieved with the above searches, and used as source for individual studies: Thomas, 2000
Search date	6 March 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Bachert, 2005, Belgium	Experimental: Randomized controlled trial	392 patients from Ukraine and Russia, 201 male, 191 female, aged 18-65 years, with acute uncomplicated febrile upper respiratory tract infection (URTI). URTI had to have been present for no more than 5 days, orally measured body temperature between 38.5°C and 40°C, and other symptoms of URTI (eg.	1. Aspirin 500 mg 2. Aspirin 1000 mg 3. Acetaminophen 500 mg 4. Acetaminophen 1000 mg 5. Placebo [data on aspirin will not be extracted]	Sample size was calculated to be 450 (90 patients per treatment) to obtain 80% power.

		Sore throat) had to be present. In an ITT population, patients received 500 mg or 1000 mg aspirin (n=78), 500 or 1000 mg acetaminophen (=paracetamol) (n=79) or placebo (n=78)		
Bertin, 1991, France	Experimental: Randomized controlled trial	231 children (127 male, 104 female), aged 6-12 years (mean age 7.95±1.85 years). Duration of sore throat had to be no more than 48 hours. Patients were randomly assigned to one of three parallel treatment groups: ibuprofen (n=77), acetaminophen (n=78) or placebo (n=76).	1. Ibuprofen 2. Acetaminophen 3. Placebo Drugs were given orally at a dosage of 10 mg/kg three times daily for 48 hours, as identical-looking microgranules. [data for ibuprofen were not extracted]	
Burnett, 2006, USA	Experimental: Randomized controlled trial	241 patients (95 male, 146 female), mean age 20 years, with acute sore throat. Patients were randomized to receive either paracetamol containing sodium bicarbonate (n=181) or placebo (n=60)	1. Paracetamol 500 mg with sodium bicarbonate (PSC) 2. Placebo	Sample size was estimated: with a total sample size of 240 patients (using a treatment allocation ratio of 3:1), the study had 90% power to detect differences in time to onset of analgesia of ≥13 minutes)
Schachtel, 1988, USA	Experimental: Randomized controlled trial	120 patients (50 male, 70 female), aged 18-88 years, with relatively severe sore throat pain (score >66 mm on the 100 mm Sore Throat Pain Intensity Scale) and objective evidence of tonsillopharyngitis (score of 4 or more on the 10-point tonsillopharyngitis assessment). Patients were randomized to receive ibuprofen (n=39), paracetamol (n=40) or placebo (n=41). The Sore Throat Pain Intensity Scale was analysed at individual time points as the absolute difference (PID) and the sum of pain intensity differences at 6h (SPID). Total pain relief at 6h = TOTPAR.	1. Ibuprofen: 400 mg 2. Paracetamol: 1000 mg acetaminophen 3. Placebo: inert ingredients [data on ibuprofen were not extracted]	

Schachtel, 1993, USA	Experimental: Randomized controlled trial	116 children (57 male, 59 female), mean age 8.7 years (range 3.5-12.5 years) with acute sore throat (score >100 mm on the 200 mm Children's Sore Throat Pain Thermometer). Children were randomly assigned to ibuprofen suspension 20 mg/ml (n=39), acetaminophen suspension 32 mg/ml (n=39) or placebo vehicle control (n=39)	1. Ibuprofen suspension: 10 mg/kg 2. Paracetamol: 15 mg/kg acetaminophen suspension 3. Placebo vehicle control	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Sore throat (ordinal scale)	1. Acetaminophen 500 mg 2. Acetaminophen 1000 mg 3. Placebo	Not statistically significant: 1 vs 3: 3.22±2.73 vs 3.26±2.57 MD:-0.04, 95%CI [-0.87, 0.79] (p=0.92)* 2 vs 3: 3.49±2.51 vs 3.26±2.57 MD:0.23, 95%CI [-0.56, 1.02], p=0.57*	1, 79 vs 79 vs 78 §	Bachert, 2005
Sore throat/time point (ordinal scale)		<u>2 hours</u>: Not statistically significant: 1 vs 3: 2.77±2.41 vs 3.08±2.36 MD:-0.31, 95%CI [-1.06, 0.44] (p=0.42)* 2 vs 3: 2.95±2.31 vs 3.08±2.36 MD:-0.13, 95%CI [-0.86, 0.60] (p=0.73)* <u>4 hours</u>: Not statistically significant: 1 vs 3: 2.61±2.29 vs 2.95±2.37 MD:-0.34, 95%CI [-1.07, 0.39] (p=0.36)* 2 vs 3: 2.70±2.19 vs 2.95±2.37 MD:-0.25, 95%CI [-0.96, 0.46] (p=0.49)* <u>6 hours</u>: Not statistically significant: 1 vs 3: 2.80±2.41 vs 3.01±2.33 MD:-0.21, 95%CI [-0.95, 0.53] (p=0.58)*		

		2 vs 3: 2.68±2.17 vs 3.01±2.33 MD:-0.33, 95%CI [-1.03, 0.37] (p=0.36)*		
Spontaneous pain resolved	1. Paracetamol 2. Placebo	Not statistically significant: 70.5% (55/78) vs 55% (42/76) RR: 1.28, 95%CI [1.00, 1.64] (p=0.05)* ¥	1, 78 vs 76 §	Bertin, 1991
Pain while swallowing resolved		Statistically significant: 64% (49/78) vs 43% (33/76) RR: 1.45, 95%CI [1.06, 1.97] (p=0.02)* *In favour of acetaminophen*		
Analgesia (Sore Throat Relief Score)		Statistically significant: 15 min after dosing 0.41 vs 0.19 (p≤0.03) Significant difference remains for every time point thereafter. (Data represented in graph, no SD, effect size and CI available †) *In favour of paracetamol*	1, 181 vs 60	Burnett, 2006
Sum of pain intensity differences at 6h (SPID)		Statistically significant: 195.6±98.9 vs 9.3±26.9 MD: 186.30, 95%CI [154.56, 218.04] (p<0.00001)* *In favour of paracetamol*	1, 40 vs 41 §	Schachtel, 1988
		Statistically significant: 274.6±295.2 vs 105.2±247.2 MD: 169.40, 95%CI [47.63, 291.17] (p=0.006)* *In favour of paracetamol*	1, 38 vs 39 §	Schachtel, 1993
Total pain relief at 6h (TOTPAR)		Statistically significant: 13.6±5.9 vs 0.6±1.5 MD: 13.00, 95%CI [11.11, 14.89] (p<0.00001)* *In favour of paracetamol*	1, 40 vs 41 §	Schachtel, 1988
		Statistically significant: 9.2±7.0 vs 5.6±5.6 MD: 3.60, 95%CI [0.76, 6.44] (p=0.01)* *In favour of paracetamol*	1, 38 vs 39 §	Schachtel, 1993
Change in swollen throat		Statistically significant: 146.3±104.7 vs 5.2±47.2 MD: 141.10, 95%CI [105.58, 176.62] (p<0.00001)* *In favour of paracetamol*	1, 40 vs 41 §	Schachtel, 1988
Change in difficulty swallowing		Statistically significant: 166.5±105.0 vs -0.2±35.7 MD: 166.70, 95%CI [132.37, 201.03] (p<0.00001)* *In favour of paracetamol*		

Mean ± SD (unless otherwise indicated)

* Calculations done by the reviewer(s) using Review Manager software

¥ Imprecision (large variability of results)

† Imprecision (lack of data)

§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Bachert, 2005	No, permuted block randomization	No	No	No	
Bertin, 1991	No, computer-generated randomization list was given to each centre	No, drugs were given as identical-looking micro-granules	No	No	
Burnett, 2006	Unclear	No, placebo and paracetamol were matched	No	No	Conflict of interest: study paid by and performed by employees of GSK
Schachtel, 1988	No, computer-generated randomization code	Unclear, double-blind, but not mentioned how	No	No	
Schachtel, 1993	No, computer-generated randomization code	No, medications were identical in colour, aroma, taste and consistency	No	No	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes, lack of data
Inconsistency	0	
Indirectness	0	
Publication bias	-1	Conflict of interest
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is limited evidence from 5 experimental studies in favour of paracetamol. It was shown that paracetamol resulted in a statistically significant decrease of pain while swallowing and pain intensity, and a statistically significant increase in pain relief and change in swollen throat, compared to placebo (Bertin 1991, Burnett 2006, Schachtel 1988, Schachtel 1993). A statistically significant change of sore throat (ordinal outcome), sore throat/time point or spontaneous pain, using paractemol compared to placebo, could not be demonstrated (Bachert 2005, Bertin 1991). Evidence is of low quality and results cannot be considered precise due to limited sample size and/or large variability of results.
Reference(s)	**Articles** Bachert C, Chuchalin AG, Eisebitt R, Netayzhenko VZ, Voelker M. *Aspirin compared with acetaminophen in the treatment of fever and other symptoms of upper respiratory tract infection in adults: a multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel-group, single-dose, 6-hour dose-ranging study*. Clin Ther 2005, 27(7):993-1003 Bertin L, Pons G, d'Athis P, Lasfargues G, Maudelonde C, Duhamel JF, Olive G. *Randomized, double-blind, multicenter, controlled trial of ibuprofen versus acetaminophen (paracetamol) and placebo for treatment of symptoms of tonsillitis and pharyngitis in children*. J Pediatr 1991, 119(5):811-14.

	Burnett I, Schachtel B, Sanner K, Bey M, Grattan T, Littlejohn S. *Onset of analgesia of a paracetamol tablet containing sodium bicarbonate: A double-blind, placebo-controlled study in adult patients with acute sore throat*. Clin Ther 2006, 28(9):1273-78. Schachtel BP, Fillingim JM, Thoden WR, Lane AC, Baybutt RI. *Sore throat pain in the evaluation of mild analgesics.* Clin Pharmacol.Ther 1988, 44(6):704-11. Schachtel BP, Thoden WR. *A placebo-controlled model for assaying systemic analgesics in children.* Clin Pharmacol.Ther 1993, 53(5):593-601.

Headache – Paracetamol (First Aid)

Question (PICO)	In persons with headache (P) is taking paracetamol (I) compared to no intervention (C) effective to improve symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh headache] OR headache:ti,ab,kw 2. [mh acetaminophen] OR paracetamol:ti,ab,kw OR acetaminophen:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Headache[Mesh] OR headache[TIAB] 2. Acetaminophen[Mesh] OR paracetamol[TIAB] OR acetaminophen[TIAB] 3. ((((((((((Meta-Analysis as Topic[Mesh])) OR ((meta analy*[TIAB]))) OR ((metaanaly*[TIAB]))) OR ((Meta-Analysis[Publication Type]))) OR ((systematic review*[TIAB] OR systematic overview*[TIAB]))) OR ((Review Literature as Topic[Mesh])))) OR ((cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB]))) OR ((reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB]))) OR ((((selection criteria[TIAB] OR data extraction[TIAB])) AND ((Review[PT]))))) NOT ((Comment[PT] OR Letter[PT] OR Editorial[PT] OR animal[Mesh] NOT (animal[Mesh] AND human[Mesh]))) 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'headache'/exp OR headache:ab,ti 2. acetaminophen:ab,ti OR paracetamol:ab,ti 3. 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti 4. 1-2 AND Guidelines, systematic reviews, retrieved with the above searches, and used as source for individual studies: Derry, 2013 Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	11 March 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages.

	Intervention: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Only studies were included who compared paracetamol with placebo. Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. Studies that compared paracetamol with another analgesic agent were excluded. **Outcome**: Include: functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Freitag, 2008, USA	Experimental: Randomized controlled trial	173 participants (21 male, 152 female), mean age 43 years, with migraine ± aura. Patients were treated with paracetamol (n=43), Rizatriptan (n=43), Rizatriptan + paracetamol (n=48), placebo (n=39). Single attack was treated with single dose of medication.	1. Paracetamol: 1000 mg 2. Riatriptan: 10 mg 3. Rizatriptan + paracetamol: 10/1000 mg 4. Placebo [only data on paracetamol were extracted]	This study is cited in the Cochrane Review: Derry, 2013
Hoernecke, 1993, Germany	Experimental: Randomized controlled trial (within subjects)	288 participants (55 male, 233 female), mean age 42 years, with "simple" migraine. Patients were treated with paracetamol, Dihydroergotamine, Paracetamol + dihydroergotamine, Placebo. Numbers in each group not mentioned	1. Paracetamol: 1000 mg 2. Dihydroergotamine: 2 mg 3. Paracetamol + dihydroergotamine: 1000/2 mg 4. Placebo [data on dihydroergotamine were not extracted]	This study is cited in the Cochrane Review: Derry, 2013

Lipton, 2000, USA	Experimental: Randomized controlled trial	289 participants (58 male, 231 female), mean age 37 years, with migraine ± aura. Patients were treated with paracetamol (n=147) or placebo (n=142)	1. Paracetamol: 1000 mg 2. Placebo	This study is cited in the Cochrane Review: Derry, 2013
Prior, 2010, USA	Experimental: Randomized controlled trial	346 participants (58 male, 288 female), mean age 39 years, with episodic migraine ± aura. Patients were treated with paracetamol (n=177) or placebo (n=169). Prophylactic medication continued unchanged.	1. Paracetamol: 1000 mg 2. Placebo	This study is cited in the Cochrane Review: Derry, 2013

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Pain free at 2 hours	Paracetamol vs placebo	Moderate/severe pain: Statistically significant: 68/367 vs 36/350 RR: 1.80, 95%CI [1.24, 2.62] (p=0.0022) *In favour of paracetamol*	3, 367 vs 350 §	Freitag 2008, Lipton 2000, Prior 2010 (cited in Derry 2013)
		Onset of attack: Statistically significant: 89/288 vs 65/288 RR: 1.37, 95%CI [1.04, 1.80] (p=0.025) *In favour of paracetamol*	1, 288 vs 288 § (within subjects)	Hoernecke, 1993 (cited in Derry 2013)
Headache relief at 1 hour		Statistically significant: 127/324 vs 62/311 RR: 1.97, 95%CI [1.52, 2.55] (p<0.00001) *In favour of paracetamol*	2, 324 vs 311 §	Lipton 2000, Prior 2010 (cited in Derry 2013)
Headache relief at 2 hours		Moderate/severe pain: Statistically significant: 207/367 vs 127/350 RR: 1.55, 95%CI [1.32, 1.83] (p<0.00001) *In favour of paracetamol*	3, 367 vs 350	Freitag 2008, Lipton 2000, Prior 2010 (cited in Derry 2013)
		Onset of attack: Statistically significant: 109/288 vs 56/288 RR: 1.95, 95%CI [1.47, 2.57] (p<0.00001) *In favour of paracetamol*	1, 288 vs 288 § (within subjects)	Hoernecke, 1993 (cited in Derry 2013)
Any adverse events		Statistically significant: 117/655 vs 144/638 RR: 0.78, 95%CI [0.64, 0.95] (p=0.013) *In favour of paracetamol*	4, 655 vs 638 §	Freitag 2008, Hoernecke 1993, Lipton 2000, Prior 2010 (cited in Derry 2013)
Use of rescue medication at 6 h		Statistically significant: 79/324 vs 129/311 RR: 0.59, 95%CI [0.47, 0.74] (p<0.00001)	2, 324 vs 311 §	Lipton 2000, Prior 2010 (cited in Derry 2013)

		In favour of paracetamol		
Relief of functional disability at 2 hours		Statistically significant: 74/309 vs 41/301 RR: 1.76, 95%CI [1.24, 2.48] (p=0.0014) *In favour of paracetamol*	2, 309 vs 301 §	Lipton 2000, Prior 2010 (cited in Derry 2013)

Mean ± SD (unless otherwise indicated)
§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Freitag, 2008	No, computer-generated	No, double-dummy, matched placebos	No, dropouts described	No	
Hoernecke, 1993	No, randomization order in form of Latin square	Unclear, not described	Yes (see Derry 2013)	No	
Lipton, 2000	No, computer-generated randomization schedule	No, identical appearing placebo tablets	No, dropouts described	No	
Prior, 2010	No, computer-generated randomization code	No, tablets identical in size, shape and colour	No, adequate reasons for exclusion given	No	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Low number of events
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Moderate [B]**	

Conclusion	There is limited evidence from 4 experimental studies in favour of paracetamol. It was shown that paracetamol resulted in a statistically significant decrease of headache, adverse events, functional disability, compared to placebo, use of rescue medication (Freitag 2008, Hoernecke 1993, Lipton 2000, Prior 2010). Evidence is of moderate quality and results cannot be considered precise due to low number of events.
Reference(s)	**Articles** Freitag F, Diamond M, Diamond S, Janssen I, Rodgers A, Skobieranda F. *Efficacy and tolerability of coadministration of rizatriptan and acetaminophen vs riatriptan or acetaminophen alone for acute migraine treatment.* Headache 2008, 48(6): 921-30. Hoernecke R, Doenicke A. *Treatment of migraine attacks: combination of dihydroergotamine tartrate and paracetamol in comparison with individual drugs and placebo*. Medizinische Klinik (Munich) 1993, 88(11): 642-8. Lipton RB, Baggish JS, Stewart WF, Codispoti JR, Fu M. *Efficacy and safety of acetaminophen in the treatment of migraine. Results of a randomized, double-blind, placebo-controlled, population-based study*. Archives of Internal Medicine 2000, 160(22): 3489-92. Prior MJ, Codispoti JR, Fu M. *A randomized, placebo-controlled trial of acetaminophen for treatment of migraine headache*. Headache 2010, 50(5): 819-33. **Systematic reviews**

	Derry S, Moore RA. *Paracetamol (acetaminophen) with or without antiemetic for acute migraine headaches in adults*. Cochrane Database of Systematic Reviews 2013, Issue 4. Art No.: CD008040.

Headache – Cool and dark environment (First Aid)

Question (PICO)	In humans with a headache (P), is resting in a cool and dark environment (I) compared to not doing this (C) effective to decrease the headache?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh headache] OR headache:ti,ab,kw 2. Cool:ti,ab,kw OR dark:ti,ab,kw OR quiet:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Headache[Mesh] OR headache[TIAB] 2. Cool[TIAB] OR dark[TIAB] OR quiet[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'headache'/exp OR headache:ab,ti 2. Cool:ab,ti OR dark:ab,ti OR quiet:ab,ti 3. 1-2 AND
Search date	14 August 2015
In/Exclusion criteria	**Population**: people with headaches **Intervention**: resting in a cool, dark, quiet environment **Comparison**: not resting in a cool, dark, quiet environment **Outcome**: resolution of pain. **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

CHEST

Myocardial infarction – Body position (First aid)

Question (PICO)	Among persons with myocardial infarction (P), does a certain posture (I) compared to another posture (C) change functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health-related outcomes (O)?
Search Strategy	Databases **The Cochrane Library** using the following search strategy: 1. [mh acute coronary syndrome] OR [mh coronary disease] OR [mh myocardial infarction] 2. [mh posture] OR 'posture':ti,ab,kw OR 'postures':ti,ab,kw 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'ischemic heart disease'/exp 2. 'body posture'/exp OR posture:ab,ti OR postures:ab,ti 3. 1-2 AND **MEDLINE** (via PubMed interface) using the following search strategy: 1. "coronary artery disease"[Mesh] OR "myocardial infarction"[Mesh] OR "acute coronary syndrome"[Mesh] 2. postures[tiab] OR posture[tiab] OR "Posture"[Mesh] 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	17 February 2015
In/Exclusion criteria	**Population:** Include: patients with a myocardial infarction/coronary heart disease in an acute setting Exclude: we excluded studies on patients with coexisting valvular heart diseases, chronic heart failure and/or arrhythmias. Also patients with coronary artery disease recruited in a non-acute setting were excluded. **Intervention:** Include: any body position that can be provided by lay people. Exclude: any body position that cannot be provided by lay people (e.g. Trendelenburg position). **Comparison:** Include: studies that compare different body positions **Outcome:** Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Study design:** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomized controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year:** Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Reich, 1989, USA	Experimental: Randomized trial (within subjects design: cross-over)	18 anesthetized patients undergoing myocardial revascularization were studied. All patients had two to three vessel coronary artery disease with a left ventricular ejection fraction ≥0.4. All patients had experienced prior myocardial infarctions. The average age was 62 yr, 10 patients were male, 10 were taking ß-blockers and nine were taking calcium channel-blockers.	Intervention: passive straight leg raising (60°) Control: Supine position The order of the study positions was varied randomly. There was always a 5-minutes period in the supine position.	The study commenced 10 minutes after endotracheal intubation and no surgical stimulation took place during the study. Data about the Trendelenburg position were not extracted. This intervention is not feasible for lay people

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Cardiac index (cardiac output divided by the body surface area, L/min/m^2)	Passive straight leg raising (60°) versus supine position	Not statistically significant: 2.37±0.73 vs 2.36±0.79, no effect size/CI available (p>0.05)	1,18 vs 18 § (within subjects design)	Reich,1989
Right-ventricular ejection fraction		Statistically significant: 0.41±0.10 vs 0.48±0.11, (p<0.05) *In favour of the supine position*		

Mean ± SD
§ Imprecision (limited sample size)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Reich,1989	No	No	No	No	Within subjects design

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Limited sample size
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Moderate [B]**	

Conclusion	There is limited evidence neither in favour of passive straight leg raising (60°) nor the supine position. In this evidence conclusion, we place a higher value on outcomes related to left ventricular function compared to the right ventricular function. A statistical significant difference in the left ventricular function (i.e. cardiac index) between passive straight leg raising and the supine position could not be demonstrated (Reich, 1989). However, this study also showed that passive straight leg raising (60°) resulted in a statistically significant (but clinically no meaningful) reduced right ventricular function (right ventricular ejection fraction). Evidence is of moderate quality and results of this study is imprecise due to limited sample size.
Reference(s)	**Articles:** Reich DL, Konstadt SN, Raissi S, Hubbard M, Thys DM. *Trendelenburg position and passive leg raising do not significantly improve cardiopulmonary performance in the anesthesized patient with coronary artery disease*. Crit Care Med 1989,17:313-317

Myocardial infarction – Clinical signs/symptoms (Diagnostics)

Question (PICO)	Among persons with chest discomfort (P), are some symptoms (I) more predictive than others (C) for the diagnosis of myocardial infarction (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews) using the following search strategy: 1. [mh meta-analysis] OR meta analys*:ti,ab,kw OR meta-analys*:ti,ab,kw OR 'cochrane':ti,ab,kw OR 'embase':ti,ab,kw OR 'pubmed':ti,ab,kw OR 'medline':ti,ab,kw OR 'reference list':ti,ab,kw OR 'reference lists':ti,ab,kw OR 'bibliography':ti,ab,kw OR 'bibliographies':ti,ab,kw OR 'hand-search':ti,ab,kw OR 'manual search':ti,ab,kw OR 'selection criteria':ti,ab,kw OR 'relevant journals':ti,ab,kw 2. [mh acute coronary syndrome] OR [mh coronary disease] OR [mh myocardial infarction] 3. 'pain':ti,ab,kw and 'chest':ti,ab,kw 4. 1-3 AND **Embase** (via Embase.com interface) for systematic reviews using the following search strategy: 1. 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti 2. 'acute coronary syndrome'/exp or 'heart infarction'/exp 3. 'pain':ab,ti and 'chest':ab,ti 4. 1-3 AND **MEDLINE** (via PubMed interface) for systematic reviews using the following search strategy: 1. "Guideline "[Publication Type] OR "Practice Guidelines as Topic"[Mesh] OR "Practice Guideline "[Publication Type] OR practice guideline*[TIAB])) OR Meta-Analysis as Topic[Mesh] OR meta analy*[TIAB] OR metaanaly*[TIAB] OR Meta-Analysis[Publication Type] OR systematic review*[TIAB] OR systematic overview*[TIAB] OR Review Literature as Topic[Mesh] OR cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB])) OR reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB] OR selection

	criteria[TIAB] OR data extraction[TIAB] AND Review[PT] NOT Comment[PT] OR Letter[PT] OR Editorial[PT] OR animal[Mesh] NOT animal[Mesh] AND human[Mesh] 2. "Acute Coronary Syndrome/diagnosis"[Mesh] OR "Myocardial Infarction/diagnosis"[Mesh] OR "Coronary Artery Disease/diagnosis"[Mesh] 3. "Chest"[TIAB] AND "pain"[TIAB] 4. 1-3 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	13 February 2015
In/Exclusion criteria	**Population:** Include: subjects with (suspected) symptoms/signs for the diagnosis of an acute myocardial infarction. Subjects were recruited by general practitioners, paramedics, emergency departments, coronary care units and/or cardiologists. Exclude: subjects with chronic chest pain, subjects diagnosed as having coronary artery disease or acute coronary syndrome. **Intervention:** Include: clinical symptoms/signs suggestive for acute myocardial infarction which can be detected by lay people (i.e. basic first responders, lay caregivers and/or community health workers). Only symptoms with data for a 2x2 table were considered Exclude: clinical symptoms suggestive for acute myocardial infarction which cannot be detected by lay people (i.e. basic first responders, lay caregivers and/or community health workers). **Comparison:** Include: a diagnostic reference method for the diagnosis of an acute myocardial infarction (e.g. elevated cardiac isoenzyme levels, diagnostic changes on the ECG, history, scintigraphy, autopsy, criteria of the World Health Organization or European Society of Cardiology, sudden death, coronary angiography, echocardiography, urgent revascularization. In some studies, at least 2 tests were required. History alone was always insufficient to diagnose an acute myocardial infarction. Exclude: studies not using a diagnostic reference method. **Outcome:** Include: Diagnostic-related outcomes such as sensitivity, specificity, positive/negative predictive value and/or positive/negative likelihood ratio (pLR/nLR). Likelihood ratios were considered as the preferred measure of diagnostic accuracy since they are clinically more meaningful than sensitivities, specificities, or diagnostic odds ratios. They quantify how strongly the likelihood of a disease is changed by the presence (pLR) or absence (nLR) of a symptom or sign. A LR of 1 indicates a test result without any diagnostic value. LRs of 1 to 2 or 0.5 to 1 change the likelihood very little and they are rarely important. LRs ≤0.5 or ≥2 change it at least moderately and can be considered as clinically helpful in the context of medical history taking and physical examination. **Study design:** Include: a systematic review/meta-analysis when the search strategy and selection criteria are clearly described and if at least MEDLINE was searched. Exclude: Systematic reviews that did not report data of the individual studies separately were not included. Individual experimental/observational studies, case series, cross-sectional studies, animal studies, *ex vivo* or *in vitro* studies were also excluded. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year:** Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Bruyninckx, 2008, Belgium	Systematic review of 28 diagnostic accuracy studies	Subjects with symptoms for the diagnosis of an acute myocardial infarction. Only subjects which were recruited by general practitioners,	Index test: 1. pain radiating to left arm and/or shoulder 2. pain radiating to right arm and/or shoulder 3. pain radiating to both arms and/or shoulders 4. pain radiating to neck	The acceptance of a broad range of inclusion criteria (autopsy, sudden death, scintigraphy, echocardiography, and angiography) as

		paramedics or emergency departments) were included. Subjects recruited by coronary care units or cardiologists were excluded.	5. pain radiating to back 6. epigastric pain 7. oppressive pain 8. nausea and/or vomiting 9. sweating 10. absence of tenderness Reference standard: Enzyme rises (n=23), electrocardiogram (ECG) change (n=22), history (n=11), scintigraphy (n=8), autopsy (n=5), criteria of the World Health Organization or European Society of Cardiology (n=4), sudden death (n=3), coronary angiogram (n=2), echocardiography (n=2), or urgent revascularisation (n=1). In some studies, at least two tests were required. History alone was always insufficient to diagnose an acute myocardial infarction.	reference tests increased the number of real positives at the risk of spectrum bias
Chun, 2004, USA	Systematic review of 7 diagnostic accuracy studies	Subjects presented to emergency departments complaining of chest pain that was unrelated to trauma and unexplained by the chest radiograph. Most patients were hospitalized in telemetry or coronary care units for further monitoring and testing	Index test: Symptoms suggestive for myocardial infarction (quality of pain, timing of pain, pain location, associated symptoms) Reference standard: elevated cardiac isoenzyme levels and/or diagnostic changes on the ECG.	
Haasenritter, 2012, Germany	Systematic review of 172 diagnostic accuracy studies	Patients presenting with acute or chronic chest pain. The target disease was coronary heart disease, with no restrictions regarding case definitions, e.g. stable coronary heart disease, acute coronary syndrome, myocardial	Index test: any items of physical examination or medical history like pain characteristics or associated symptoms. Reference standard: clinical course and/or elevated cardiac isoenzyme levels	

		infarction, or major cardiac event.		

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Pain location				
Diagnosis of myocardial infarction: positive likelihood ratio	Pain in right arm and/or shoulder versus reference standard	Positive likelihood ratio (LR+) 2.89, 95% CI [1.40;5.98] *index test can be considered as clinically helpful for the presence of myocardial infarction*	1,492 (SR of diagnostic accuracy studies)	Bruyninckx, 2008
		Positive likelihood ratio (LR+) 4.7, 95% CI [1.90;12.0] *index test can be considered as clinically helpful for the presence of myocardial infarction*	2,770 (SR of diagnostic accuracy studies)	Chun, 2004
		Positive likelihood ratio (LR+) 4.43, 95% CI [1.77;11.10] *index test can be considered as clinically helpful for the presence of myocardial infarction*	6,2090 (SR of diagnostic accuracy studies)	Haasenritter, 2012
	Pain in left arm and/or shoulder versus reference standard	LR+ 1.42, 95% CI [1.10 to 1.83] *index test can be considered as not clinically helpful for the presence of myocardial infarction*	1,2204 (SR of diagnostic accuracy studies)	Bruyninckx, 2008
		LR+ 1.40, 95% CI [1.30 to 1.50] *index test can be considered as not clinically helpful for the presence of myocardial infarction*	1,7734 (SR of diagnostic accuracy studies)	Chun, 2004
	Pain in both arms versus reference standard	LR+ 2.35, 95% CI [1.44 to 3.84] *index test can be considered as clinically helpful for the presence of myocardial infarction*	1,137 (SR of diagnostic accuracy studies)	Bruyninckx, 2008
	Pain in neck versus reference standard	LR+ 1.48, 95% CI [0.94 to 2.31] *index test can be considered as not clinically helpful for the presence of myocardial infarction*	1,2204 (SR of diagnostic accuracy studies)	
	Pain in back versus reference standard	LR+ 0.84, 95% CI [0.62 to 1.14] *index test can be considered as not clinically helpful for the presence of myocardial infarction*	3,1537 (SR of diagnostic accuracy studies)	
	Epigastric pain versus reference standard	LR+ 1.44, 95% CI [0.73 to 2.83] *index test can be considered as not clinically helpful for the presence of myocardial infarction*	1,596 (SR of diagnostic accuracy studies)	
	Substernal pain versus reference standard	LR+ 1.20, 95% CI [1.10 to 1.30] *index test can be*	2,7934 (SR of diagnostic	Chun, 2004

		considered as not clinically helpful for the presence of myocardial infarction	accuracy studies)	
	Central chest pain versus reference standard	LR+ 1.23, 95% CI [1.10 to 1.38] *index test can be considered as not clinically helpful for the presence of myocardial infarction*	9,10788 (SR of diagnostic accuracy studies)	Haasenritter, 2012
	Right-sided chest pain versus reference standard	LR+ 1.39, 95% CI [0.58 to 3.34] *index test can be considered as not clinically helpful for the presence of myocardial infarction*	3,1635 (SR of diagnostic accuracy studies)	
	Visceral pain versus reference standard	LR+ 1.21, 95% CI [0.89 to 1.63] *index test can be considered as not clinically helpful for the presence of myocardial infarction*	10,13194 (SR of diagnostic accuracy studies)	
Quality of pain				
Diagnosis of myocardial infarction	Oppressive pain versus reference standard	LR+ 1.42, 95% CI [1.32 to 1.53] *index test can be considered as not clinically helpful for the presence of myocardial infarction*	5,13720 (SR of diagnostic accuracy studies)	Bruyninckx, 2008
		LR+ 1.30, 95% CI [1.20 to 1.50] *index test can be considered as not clinically helpful for the presence of myocardial infarction*	7,11504 (SR of diagnostic accuracy studies)	Chun, 2004
	Severe pain versus reference standard	LR+ 1.80, 95% CI [0.90 to 3.80] *index test can be considered as not clinically helpful for the presence of myocardial infarction*	2,596 (SR of diagnostic accuracy studies)	
	Sharp pain versus reference standard	LR+ 0.30, 95% CI [0.20 to 0.50] *index test can be considered as clinically helpful for the absence of myocardial infarction*	2,1088 (SR of diagnostic accuracy studies)	
	Burning, indigestion versus reference standard	LR+ 1.40, 95% CI [0.70 to 2.80] *index test can be considered as not clinically helpful for the presence of myocardial infarction*	1,596 (SR of diagnostic accuracy studies)	
		LR+ 1.35, 95% CI [0.87 to 2.09] *index test can be considered as not clinically helpful for the presence of myocardial infarction*	5,2047 (SR of diagnostic accuracy studies)	Haasenritter, 2012
	Aching versus reference standard	LR+ 0.70, 95% CI [0.40 to 1.30] *index test can be considered as not clinically helpful for the presence of myocardial infarction*	1,596 (SR of diagnostic accuracy studies)	Chun, 2004
	Positional pain versus reference standard	LR+ 0.30, 95% CI [0.20 to 0.50] *index test can be considered as clinically*	2,8330 (SR of diagnostic	

		helpful for the absence of myocardial infarction	accuracy studies)	
	Pleuritic pain versus reference standard	LR+ 0.20, 95% CI [0.20 to 0.30] *index test can be considered as clinically helpful for the absence of myocardial infarction*	3,8822 (SR of diagnostic accuracy studies)	
	Stabbing pain versus reference standard	LR+ 0.69, 95% CI [0.34 to 1.40] *index test can be considered as not clinically helpful for the presence of myocardial infarction*	6,11082 (SR of diagnostic accuracy studies)	Haasenritter, 2012
Timing of pain				
Diagnosis of myocardial infarction	Duration >60 minutes versus reference standard	LR+ 0.70, 95% CI [0.40 to 1.30] *index test can be considered as not clinically helpful for the presence of myocardial infarction*	1,278 (SR of diagnostic accuracy studies)	Chun, 2004
	Sudden onset versus reference standard	LR+ 1.10, 95% CI [0.90 to 1.30] *index test can be considered as not clinically helpful for the presence of myocardial infarction*	1,278 (SR of diagnostic accuracy studies)	
	Time since onset of pain >6h versus reference standard	LR+ 0.82, 95% CI [0.59 to 1.14] *index test can be considered as not clinically helpful for the presence of myocardial infarction*	6,12212 (SR of diagnostic accuracy studies)	Haasenritter, 2012
Associated symptoms				
Diagnosis of myocardial infarction	Vomiting and/or nausea versus reference standard	LR+ 1.41, 95% CI [1.17 to 1.72] *index test can be considered as not clinically helpful for the presence of myocardial infarction*	4,14315 (SR of diagnostic accuracy studies)	Bruyninckx, 2008
	Nausea versus reference standard	LR+ 1.70, 95% CI [1.30 to 2.30] *index test can be considered as not clinically helpful for the presence of myocardial infarction*	5,3665 (SR of diagnostic accuracy studies)	Chun, 2004
	Sweating versus reference standard	LR+ 2.92, 95% CI [1.97 to 4.32] *index test can be considered as clinically helpful for the presence of myocardial infarction*	6,13241 (SR of diagnostic accuracy studies)	Bruyninckx, 2008
		LR+ 2.10, 95% CI [1.80 to 2.50] *index test can be considered as clinically helpful for the presence of myocardial infarction*	5,11121 (SR of diagnostic accuracy studies)	Chun, 2004
	Dyspnea versus reference standard	LR+ 1.00, 95% CI [0.90 to 1.20] *index test can be considered as not clinically helpful for the presence of myocardial infarction*	2,2695 (SR of diagnostic accuracy studies)	Chun, 2004
		LR+ 0.89, 95% CI [0.76 to 1.03] *index test can be considered as not clinically*	10,11939 (SR of diagnostic	Haasenritter, 2012

		helpful for the presence of myocardial infarction	accuracy studies)	
	Palpitations versus reference standard	LR+ 0.47, 95% CI [0.28 to 0.81] *index test can be considered as clinically helpful for the absence of myocardial infarction*	5,2588 (SR of diagnostic accuracy studies)	

Data are shown as positive likelihood ratios (sensitivity/1-specificity) with 95% CI

Quality of evidence

Limitations in study design

Author, Year	Information about 'limitations of study design' from the SR
Bruyninckx,2008	Although new research on the quality of diagnostic accuracy studies confirms that quality is still not optimal, the quality of the studies included was good according to the QUADAS criteria.
Chun,2004	No information about study quality is available
Haasenritter,2012	Out of the 13 QUADAS items, only 7 referred to the whole study. Considering these items, the quality of the included studies was fair: ~50% no explanation withdrawals, ~25% no details execution reference standard, ~5% partial verification not avoided, ~10% time period between reference standard and index test not appropriate, ~15% reference standard not acceptable, ~10% selection criteria not clearly described, ~25% spectrum not representative.

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'limitations in study design'
Imprecision	0	
Inconsistency	-1	Bruyninckx 2008: "for the majority of analyses, a moderate to high level of heterogeneity was found." Chun 2004: no data about heterogeneity were reported. Haasenritter 2012: "I^2 ranged from 0 to 98.6% and was above 80% in 40 of the analyzed index tests, indicating a substantial amount of between-study heterogeneity"
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is limited evidence from 3 systematic reviews of diagnostic accuracy studies (Bruyninckx 2008, Chun 2004, Haasenritter 2012) showing that pain in the right arm/shoulder, pain in both arms and/or sweating are predictive symptoms for the presence of an acute myocardial infarction. Positional pain, pleuritic pain, sharp pain and/or palpitations could be considered as clinically helpful for the absence of an acute myocardial infarction. Finally, the following symptoms could not be considered as clinically helpful for the diagnosis of an acute myocardial infarction: pain in left arm/shoulder, pain in neck/back, epigastric pain, substernal pain, central/right-sided chest pain, visceral pain, oppressive/severe/burning/stubbing pain, aching, pain duration >60 minutes, sudden onset of pain, time since onset of pain >6 hours, vomiting, nausea or dyspnea. Evidence is of low quality.
Reference(s)	**Systematic reviews:** Bruyninckx R, Aertgeerts B, Bruyninckx P, Buntinx F. *Signs and symptoms in diagnosing acute myocardial infarction and acute coronary syndrome: a diagnostic meta-analysis.* Br J Gen Pract 2008,58:105-111. Chun AA, McGee SR. *Bedside diagnosis of coronary artery disease: a systematic review.* Am J Med 2004,117:334-343.

	Haasenritter J, Stanze D, Widera G, Wilimzig C, Abu HM, Sonnichsen AC, Bosner S, Rochon J, Donner-Banzhoff N. *Does the patient with chest pain have a coronary heart disease? Diagnostic value of single symptoms and signs--a meta-analysis.* Croat Med J 2012,53:432-441.

Hyperventilation – Breathing in a paper bag (First aid)

Question (PICO)	In people who are hyperventilating (P) is breathing in a paper bag (I) vs not doing this (C) effective to decrease symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "Hyperventilation"] OR hyperventilation:ti,ab,kw **MEDLINE** (via PubMed interface) for systematic reviews, experimental or observational studies using the following search strategy: 1. "Hyperventilation"[Mesh] 2. breathing[TIAB] OR rebreathing[TIAB] OR bag[TIAB] 3. 1 AND 2 **Embase** (via Embase.com interface) for systematic reviews, experimental or observational studies using the following search strategy using the following search strategy: 1. 'hyperventilation'/exp 2. rebreathing:ti,ab OR bag:ab,ti 3. 1 AND 2 Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	13 February 2015
In/Exclusion criteria	**Population**: Include: people with (forced) hyperventilation, or healthy volunteers of all ages. **Intervention**: Include: breathing in a paper or plastic bag or other closed breathing circuit **Comparison**: Include: not doing this **Outcome**: Include: decrease of symptoms of hyperventilation **Study design:** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
van den Houdt, 1988,	Experimental study: randomized	12 healthy undergraduate medical students	Intervention: rebreathing in a paper bag or in a	The $pACO_2$ was registered using a Gould Godart capnograph.

The Netherlands	controlled trial (within subjects design)	deliberately hyperventilating (subjects were instructed on how to hyperventilate; they breathed normally for 2 min after which they hyperventilated intensely for 2 more min)	closed circuit (after 3 min of rebreathing, subjects were asked not to rebreathe anymore but to try and ventilate normally) Control: no treatment	In order for the $pACO_2$ to be registered, subjects had to breathe through a mask covering the mouth and nose. During the intervention, the paper bag/closed circuit was attached to the capnograph mouthpiece so that restoration of the $pACO_2$ could be monitored. The closed circuit consisted of a mouthpiece to which several invisible valves were attached and was connected to a long tube. In the rebreathing condition the valves of the system were closed, while in the non-rebreathing condition they were open.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Time to reach baseline CO_2 levels (sec)	rebreathing in a paper bag vs no treatment	Statistically significant: 60 vs 450 No SDs, effect measure and CI available † ($p<0.05$) *in favour of rebreathing in bag*	1, 12 vs 12 (within subjects design) §	van den Houdt, 1988
Time to disappearance of symptoms (sec)		Statistically significant: 67 ± 42 vs 96 ± 60.2 No effect measure and CI available † ($p<0.01$) *in favour of rebreathing in bag*		
Time to reach baseline CO_2 levels (sec)	rebreathing in closed circuit vs open circuit	Statistically significant: 60 vs 300 No SD's available, CI cannot be calculated † ($p<0.05$) *in favour of rebreathing in bag*		
Time to disappearance of symptoms		Not statistically significant: 56.44 ± 45 vs 62.6 ± 31.2 No effect measure and CI available †		

Mean ± SD

† Imprecision (lack of data)

§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
van den Houdt, 1988	yes	yes	no	no	Within subjects design

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/lack of data
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is limited evidence from 1 experimental study in favour of rebreathing in a paper bag. It was shown that rebreathing in a paper bag resulted in a statistically significant decrease in time to reach baseline CO_2 levels and time to disappearance of symptoms compared to not breathing in a bag (Vandenhoudt 1988). A statistically significant decrease of the latter outcome when rebreathing in closed circuit compared to an open circuit could not be demonstrated (Vandenhoudt 1988). Evidence is of low quality and results cannot be considered precise due to limited sample size and lack of data.
Reference(s)	**Articles** van den Hout MA, Boek C, van der Molen GM, Jansen A, Griez E. *Rebreathing to cope with hyperventilation: experimental tests of the paper bag method*. J Behav Med 1988, 11(3):303-10

Hyperventilation – Calmly breathing (First Aid)

Question (PICO)	In humans who are hyperventilating (P), is calmly breathing (I) compared to not calmly breathing (C) effective and feasible change functional recovery, complications, time to resumption of usual activity, restoration to pre-exposure condition, time to resolution of symptoms or other outcome measures (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. 'breathing exercise'/exp OR 'breathing exercise':ab,ti OR 'breathing exercises':ab,ti OR 'breathing therapy':ab,ti OR 'breathing therapies':ab,ti 2. Hyperventilation/exp OR hyperventilat*:ab,ti OR 'chronic obstructive lung disease'/exp OR COPD:ab,ti OR 'chronic obstructive pulmonary disease':ab,ti OR Asthma/exp OR Asthma:ab,ti 3. 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti 4. 1-3 AND **MEDLINE** (via PubMed interface) for guidelines and systematic reviews using the following search strategy: 1. "breathing exercises"[Mesh] OR "breathing exercise"[TIAB] OR "breathing exercises"[TIAB] OR "breathing therapy"[TIAB] OR "breathing therapies"[TIAB] 2. Hyperventilation[Mesh] OR hyperventilat*[TIAB] OR "Pulmonary Disease, Chronic Obstructive"[Mesh] OR COPD[TIAB] OR "chronic obstructive pulmonary disease"[TIAB] OR Asthma[Mesh] OR Asthma[TIAB] 3. ((((((((((Meta-Analysis as Topic[Mesh])) OR ((meta analy*[TIAB]))) OR ((metaanaly*[TIAB]))) OR ((Meta-Analysis[Publication Type]))) OR ((systematic review*[TIAB] OR systematic overview*[TIAB]))) OR ((Review Literature as Topic[Mesh])))) OR ((cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR

	psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB])))) OR ((reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB])))) OR ((((selection criteria[TIAB] OR data extraction[TIAB])) AND ((Review[PT]))))))) NOT ((Comment[PT] OR Letter[PT] OR Editorial[PT] OR animal[Mesh] NOT (animal[Mesh] AND human[Mesh]))) 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'breathing exercise'/exp OR 'breathing exercise':ab,ti OR 'breathing exercises':ab,ti OR 'breathing therapy':ab,ti OR 'breathing therapies':ab,ti 2. Hyperventilation/exp OR hyperventilat*:ab,ti OR 'chronic obstructive lung disease'/exp OR COPD:ab,ti OR 'chronic obstructive pulmonary disease':ab,ti OR Asthma/exp OR Asthma:ab,ti 3. 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti 4. 1-3 AND Guidelines, systematic reviews, retrieved with the above searches, and used as source for individual studies: Barker, 2013 Jones, 2013 Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	08 July 2015
In/Exclusion criteria	**Population**: Include: Adults or children hyperventilation **Intervention**: Include: Any type of breathing exercise, such as breathing control, diaphragmatic breathing, yoga breathing, Buteyko breathing, yawn/sigh suppression,... as acute episode management Exclude: long term interventions (exercise programs lasting several weeks or months) **Comparison**: Include: no intervention or another intervention **Outcome**: Include: hyperventilation symptoms Exclude: long term outcomes such as quality of life, functional exercise capacity **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Barker, 2013, UK	Systematic review	0 studies on children with dysfunctional breathing/hyperventilation	breathing exercises vs no breathing exercises	
Jones, 2013, UK	Systematic review	1 randomized trial including adults with dysfunctional breathing/hyperventilation	relaxation therapy with breathing exercises vs relaxation therapy without breathing therapy vs no therapy	

Synthesis of findings
No studies were included in the systematic review (Barker 2013), or could be included after examination of the randomized study.

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	**Systematic reviews** Barker NJ, Jones M, O'Connell NE, Everard ML. *Breathing exercises for dysfunctional breathing/hyperventilation syndrome in children*. Cochrane Database of Systematic Reviews 2013, Art. No.: CD010376 Jones M, Harvey A, Marston L, O'Connell NE. *Breathing exercises for dysfunctional breathing/hyperventilation syndrome in adults*. Database of Systematic Reviews 2013, Art. No.:CD009041

Hyperventilation – Calmly breathing (Prevention)

Question (PICO)	In humans (P), is calmly breathing (I) compared to not calmly breathing (C) effective and feasible to prevent hyperventilation (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "breathing exercises"] OR "breathing exercise":ti,ab,kw OR "breathing exercises":ti,ab,kw OR "breathing therapy":ti,ab,kw OR "breathing therapies":ti,ab,kw 2. [mh Hyperventilation] OR hyperventilat*:ti,ab,kw OR [mh "Pulmonary Disease, Chronic Obstructive"] OR COPD:ti,ab,kw OR "chronic obstructive pulmonary disease":ti,ab,kw OR [mh Asthma] OR Asthma:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for guidelines and systematic reviews using the following search strategy: 1. "breathing exercises"[Mesh] OR "breathing exercise"[TIAB] OR "breathing exercises"[TIAB] OR "breathing therapy"[TIAB] OR "breathing therapies"[TIAB] 2. Hyperventilation[Mesh] OR hyperventilat*[TIAB] OR "Pulmonary Disease, Chronic Obstructive"[Mesh] OR COPD[TIAB] OR "chronic obstructive pulmonary disease"[TIAB] OR Asthma[Mesh] OR Asthma[TIAB] 3. ((((((((((((Meta-Analysis as Topic[Mesh])) OR ((meta analy*[TIAB]))) OR ((metaanaly*[TIAB]))) OR ((Meta-Analysis[Publication Type]))) OR ((systematic review*[TIAB] OR systematic overview*[TIAB]))) OR ((Review Literature as Topic[Mesh])))) OR ((cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB]))) OR ((reference

	list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB])) OR ((((selection criteria[TIAB] OR data extraction[TIAB])) AND ((Review[PT]))))) NOT ((Comment[PT] OR Letter[PT] OR Editorial[PT] OR animal[Mesh] NOT (animal[Mesh] AND human[Mesh]))) 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'breathing exercise'/exp OR 'breathing exercise':ab,ti OR 'breathing exercises':ab,ti OR 'breathing therapy':ab,ti OR 'breathing therapies':ab,ti 2. Hyperventilation/exp OR hyperventilat*:ab,ti OR 'chronic obstructive lung disease'/exp OR COPD:ab,ti OR 'chronic obstructive pulmonary disease':ab,ti OR Asthma/exp OR Asthma:ab,ti 3. 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti 4. 1-3 AND Guidelines, systematic reviews, retrieved with the above searches, and used as source for individual studies: Barker, 2013 Jones, 2013 Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	08 July 2015
In/Exclusion criteria	**Population**: Include: Healthy adults or children **Intervention**: Include: Any type of breathing exercise, such as breathing control, diaphragmatic breathing, yoga breathing, Buteyko breathing, yawn/sigh suppression,... as preventive measure for hyperventilation Exclude: long term interventions (exercise programs lasting several weeks or months) **Comparison**: Include: no intervention or another intervention **Outcome**: Include: hyperventilation Exclude: long term outcomes such as quality of life, functional exercise capacity **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison/Risk factor	Remarks
Barker, 2013, UK	Systematic review	0 studies on children with dysfunctional breathing/hyperventilation	breathing exercises vs no breathing exercises	
Jones, 2013, UK	Systematic review	1 randomized trial including adults with dysfunctional breathing/hyperventilation	relaxation therapy with breathing exercises vs relaxation therapy without breathing therapy vs no therapy	

Synthesis of findings
No studies were included in the systematic review (Barker 2013), or could be included after examination of the randomized study.

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	**Systematic reviews** Barker NJ, Jones M, O'Connell NE, Everard ML. *Breathing exercises for dysfunctional breathing/hyperventilation syndrome in children*. Cochrane Database of Systematic Reviews 2013, Issue 12. Art.No.: CD010376. Jones M, Harvey A, Marston L, O'Connell NE. *Breathing exercises for dysfunctional breathing/hyperventilation syndrome in adults*. Cochrane Database of Systematic Reviews 2013, Issue 5. Art. No.: CD009041.

Hyperventilation – Activity (Prevention)

Question (PICO)	In humans (P), is walking or riding a bike (I) compared to not walking or riding a bike (C) effective and feasible to prevent hyperventilation (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh hyperventilation] OR hyperventil*:ti,ab,kw 2. Distract*:ti,ab,kw OR [mh "leisure activities] OR activit*:ti,ab,kw OR [mh walking] OR walk*:ti,ab,kw OR bike:ti,ab,kw OR bicycle:ti,ab,kw OR [mh exercise] OR exercis*:ti,ab,kw OR drink*:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Hyperventilation[Mesh] OR hyperventil*[TIAB] 2. Distract*[TIAB] OR "leisure activities"[Mesh] OR activit*[TIAB] OR walking[Mesh] OR walk*[TIAB] OR bike[TIAB] OR bicycle[TIAB] OR exercise[Mesh] OR exercis*[TIAB] OR drink*[TIAB] 3. "Primary Prevention"[Mesh:NoExp] OR "Health Education"[Mesh] OR "Health Behavior"[Mesh:NoExp] OR "Preventive Medicine"[Mesh] OR "Prevention and control"[Subheading] OR prevent*[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Hyperventilation/exp OR hyperventil*:ab,ti

	2. Distract*:ab,ti OR leisure/exp OR activit*:ab,ti OR walking/exp OR walk:ab,ti OR bike:ab,ti OR bicycle:ab,ti OR exercise/exp OR exercise*:ab,ti OR drink*:ab,ti 3. 'prevention'/exp OR 'health education'/exp OR 'health behavior'/exp OR 'self examination'/de OR 'preventive medicine'/exp OR ***'prevention':lnk OR*** 'risk factor'/exp OR prevent*:ab,ti 4. 1-3 AND
Search date	24 July 2015
In/Exclusion criteria	**Population** healthy people **Intervention**: activities such as walking, riding a bike, exercises. **Comparison**: no activities **Outcome**: hyperventilation **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Hyperventilation – Distraction (Prevention)

Question (PICO)	In humans (P), is distraction (I) compared to no distraction (C) effective and feasible to prevent hyperventilation (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh hyperventilation] OR hyperventil*:ti,ab,kw 2. Distract*:ti,ab,kw OR [mh "leisure activities] OR activit*:ti,ab,kw OR [mh walking] OR walk*:ti,ab,kw OR bike:ti,ab,kw OR bicycle:ti,ab,kw OR [mh exercise] OR exercis*:ti,ab,kw OR drink*:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Hyperventilation[Mesh] OR hyperventil*[TIAB]

	2. Distract*[TIAB] OR "leisure activities"[Mesh] OR activit*[TIAB] OR walking[Mesh] OR walk*[TIAB] OR bike[TIAB] OR bicycle[TIAB] OR exercise[Mesh] OR exercis*[TIAB] OR drink*[TIAB] 3. "Primary Prevention"[Mesh:NoExp] OR "Health Education"[Mesh] OR "Health Behavior"[Mesh:NoExp] OR "Preventive Medicine"[Mesh] OR "Prevention and control"[Subheading] OR prevent*[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Hyperventilation/exp OR hyperventil*:ab,ti 2. Distract*:ab,ti OR leisure/exp OR activit*:ab,ti OR walking/exp OR walk:ab,ti OR bike:ab,ti OR bicycle:ab,ti OR exercise/exp OR exercise*:ab,ti OR drink*:ab,ti 3. 'prevention'/exp OR 'health education'/exp OR 'health behavior'/exp OR 'self examination'/de OR 'preventive medicine'/exp OR ***'prevention':lnk OR*** 'risk factor'/exp OR prevent*:ab,ti 4. 1-3 AND
Search date	24 July 2015
In/Exclusion criteria	**Population** healthy people **Intervention**: distraction **Comparison**: no distraction **Outcome**: hyperventilation **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Dyspnoea – Posture (First aid)

Question (PICO)	Among persons with dyspnoea (P), does a certain posture (I) compared to another posture (C) change functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms (O)?
Search Strategy	Databases

	The Cochrane Library (systematic reviews and controlled trials) using the following search strategy: ([mh Dyspnea] OR [mh Lung Diseases, Obstructive] OR (dyspnea):ti,ab) AND ([mh Posture] OR (posture):ti,ab OR (body position):ti,ab) **MEDLINE** (via PubMed interface) for systematic reviews, experimental or observational studies using the following search strategy: 1. "Dyspnea"[Mesh] OR Dyspnea[TIAB] OR Dyspnoea[TIAB] OR "Lung Diseases, Obstructive"[Mesh] 2. "Posture"[Mesh] OR posture[TIAB] OR "body position"[TIAB] 3. 1 AND 2 **Embase** (via Embase.com interface) for systematic reviews, experimental or observational studies using the following search strategy using the following search strategy: 1. 'dyspnea'/exp OR Dyspnea:ti,ab OR Dyspnoea:ti,ab OR 'chronic obstructive lung disease'/exp 2. 'body posture'/exp OR posture:ti,ab OR 'body position':ti,ab 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	6 March 2015
In/Exclusion criteria	**Population**: Include: people with dyspnoea (due to asthma, COPD, …) **Intervention/Comparison**: Include: Standing vs sitting or lying; Sitting vs lying **Outcome**: Include: outcomes measuring dyspnoea; Exclude: outcomes measuring lung function, lung volumes, lung capacity, respiratory muscle power, distribution of ventilation, gas transfer **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies. **Language**: English, Dutch

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
O'Neill, 1983, Canada	Experimental: non-randomized controlled trial (within subjects design)	40 patients with advanced chronic airflow limitation, during the course of an acute exacerbation. Patients having steroid treatment or with pulmonary infiltrates were excluded from the study. The patients were divided into groups with "moderate" (those with a Pi_{max}	6 different postures: standing, seated erect, seated leaning forward, supine, and right and left lateral decubitus	To assess the sensation of dyspnoea and its relief or exacerbation, a category scale was adopted. The patients were asked to categorise their shortness of breath in each position as unchanged (4-6), slightly (3-4), moderately (1-3), or markedly (0-1) better; or slightly (6-7), moderately (7-9), or markedly (9-10) worse than the sensation in the standing erect posture, which was arbitrarily chosen as the reference posture and designated as 5 on the

		greater than 35 cm $_{HO}$) and "severe" chronic airflow limitation (those having a Pi_{max} of 35 cm H2O or less in the standing position).		category scale. Only moderate or marked relief or exacerbation of the sensation of dyspnoea was classified as relief or exacerbation of dyspnoea.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
% with perceived relieved dyspnoea	Supine vs standing	Not statistically significant: Moderate: 17.7% Severe: 12.9% ££†	1, 40 vs 40 § (within subjects design)	O'Neill, 1983
	Seated erect vs standing	Not statistically significant: Moderate: 11.8% Severe: 12.9% ££†		
	Seated leaning forward vs standing	Statistically significant: Moderate: 82.6% Severe: 95.7% (p<0.001) £† *In favour of seated leaning forward position*		
	Right lateral decubitus vs standing	Not statistically significant: Moderate: 17.7% Severe: 12.9% ££†		
	Left lateral decubitus vs standing	Not statistically significant: Moderate: 17.7% Severe: 12.9% ££†		

£ No raw data and CI reported
†† No raw data, CI and p-value reported
† Imprecision (lack of data)
§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
O'Neill, 1983	Yes (no information on randomization; no allocation concealment)	Yes	No	No	Within subjects design

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/lack of data
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is limited evidence in favour of the seated leaning forward position. It was shown that being seated leaning forward resulted in a statistically significant increase of the number of patients with perceived relieved dyspnoea, compared to standing (O'Neill 1983). A statistically significant increase the number of patients with perceived relieved dyspnoea using a supine position, seated erect position, right or left lateral decubitus compared to standing, could not be demonstrated (O'Neill 1983). Evidence is of low quality and results cannot be considered precise due to limited sample size and lack of data.
Reference(s)	**Articles** O'Neill S, McCarthy DS. *Postural relief of dyspnoea in severe chronic airflow limitation: relationship to respiratory muscle strength.* Thorax 1983, 38(8):595-600

Dyspnoea – Cold humidified air (First aid)

Question (PICO)	Among persons with dyspnoea (P), does inhalation of cold/humidified air (I) compared to no inhalation of cold/humidified air (C) change functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: ([mh Dyspnea] OR (dyspnea):ti,ab) AND ([mh Cold temperature] OR (air):ti,ab,kw) **MEDLINE** (via PubMed interface) for systematic reviews, experimental or observational studies using the following search strategy: 1. "Dyspnea"[Mesh] OR Dyspnea[TIAB] 2. "Cold Temperature"[Mesh] OR "Cryotherapy"[Mesh] OR cold[TIAB] OR "Humidity"[Mesh] OR humidity[TIAB] OR "humidified air"[TIAB] 3. 1 AND 2 **Embase** (via Embase.com interface) for systematic reviews, experimental or observational studies using the following search strategy using the following search strategy: 1. 'dyspnea'/exp OR Dyspnea:ab,ti 2. 'cold'/exp OR cold:ti,ab OR 'humidity'/exp OR humidity:ti,ab OR 'humidified':ab,ti 3. air:ti,ab 4. 1-3 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	05 March 2015
In/Exclusion criteria	**Population**: Include: people with dyspnea (due to asthma, COPD, …); patients with and without a history of cold weather-associated dyspnea; patients using inhalers (but not before and during the study) **Intervention**: Include: breathing of cold air, breathing of humidified air **Comparison**: Include: not doing this **Outcome**: Include: decrease of symptoms of dyspnea **Study design:** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available.

	An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year:** Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Koskela, 1998, Finland	Experimental: randomized controlled trial (within subjects design)	14 COPD patients performing a cycle ergometer test	Intervention: cycle test at -20°C Control: cycle test at 24°C	The cycle tests were performed in random order on separate days, always at the same time of day, separated by an average of 8 days
Spence, 1993, UK	Experimental: randomized controlled trial (within subjects design)	21 COPD patients performing a cycle ergometer test	Intervention: cycle test at -13°C Control: cycle test at room temperature	Breathlessness was assessed by Borg scaling.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Dyspnoea intensity (VAS) at highest workload	Breathing air of -20°C vs 24°C	Statistically significant: 122±10 vs 102±12 £† (p<0.01) *In favour of warm air*	1, 14 vs 14 § (within subjects design)	Koskela, 1998
Breathlessness (Borg scale)	Breathing air of -13°C vs room temperature	Statistically significant: 4.1±0.5 vs 4.6±0.5 £ † (p<0.05) *In favour of cold air*	1, 21 vs 21 § (within subjects design)	Spence, 1993

Mean ± SEM

£ No effect size or CI available

† Imprecision (lack of data); § Imprecision (limited sample size)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Koskela, 1998	yes	yes	no	no	Within subjects design
Spence, 1993	yes	yes	no	no	Within subjects design

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/lack of data
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is conflicting evidence concerning inhaling cold air in case of dyspnea. It was shown that inhaling cold air compared to air at room temperature resulted in a statistically significant increase of dyspnea intensity in one study (Koskela 1998), but decreased breathlessness in another study (Spence 1993). Evidence is of low quality and results cannot be considered precise due to limited sample size or lack of data.
Reference(s)	**Articles:** Koskela H, Pihlajamäki J, Pekkarinen H, Tukiainen H. *Effect of cold air on exercise capacity in COPD: increase or decrease?* Chest 1998, 113(6):1560-5 Spence DP, Graham DR, Ahmed J, Rees K, Pearson MG, Calverley PM. *Does cold air affect exercise capacity and dyspnea in stable chronic obstructive pulmonary disease*? Chest 1993, 103(3):693-6

Asthma and COPD – calmly breathing (First Aid)

Question (PICO)	In humans with asthma or COPD (P), is calmly breathing (I) compared to not calmly breathing (C) effective and feasible change functional recovery, complications, time to resumption of usual activity, restoration to pre-exposure condition, time to resolution of symptoms or other outcome measures (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. 'breathing exercise'/exp OR 'breathing exercise':ab,ti OR 'breathing exercises':ab,ti OR 'breathing therapy':ab,ti OR 'breathing therapies':ab,ti 2. Hyperventilation/exp OR hyperventilat*:ab,ti OR 'chronic obstructive lung disease'/exp OR COPD:ab,ti OR 'chronic obstructive pulmonary disease':ab,ti OR Asthma/exp OR Asthma:ab,ti 3. 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti 4. 1-3 AND **MEDLINE** (via PubMed interface) for guidelines and systematic reviews using the following search strategy: 1. "breathing exercises"[Mesh] OR "breathing exercise"[TIAB] OR "breathing exercises"[TIAB] OR "breathing therapy"[TIAB] OR "breathing therapies"[TIAB] 2. Hyperventilation[Mesh] OR hyperventilat*[TIAB] OR "Pulmonary Disease, Chronic Obstructive"[Mesh] OR COPD[TIAB] OR "chronic obstructive pulmonary disease"[TIAB] OR Asthma[Mesh] OR Asthma[TIAB] 3. ((((((((((Meta-Analysis as Topic[Mesh])) OR ((meta analy*[TIAB]))) OR ((metaanaly*[TIAB]))) OR ((Meta-Analysis[Publication Type]))) OR ((systematic review*[TIAB] OR systematic overview*[TIAB]))) OR ((Review Literature as Topic[Mesh])))) OR ((cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB]))) OR ((reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB]))) OR ((((selection criteria[TIAB] OR data extraction[TIAB])) AND ((Review[PT]))))))) NOT ((Comment[PT] OR Letter[PT] OR Editorial[PT] OR animal[Mesh] NOT (animal[Mesh] AND human[Mesh]))) 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy:

	1. 'breathing exercise'/exp OR 'breathing exercise':ab,ti OR 'breathing exercises':ab,ti OR 'breathing therapy':ab,ti OR 'breathing therapies':ab,ti 2. Hyperventilation/exp OR hyperventilat*:ab,ti OR 'chronic obstructive lung disease'/exp OR COPD:ab,ti OR 'chronic obstructive pulmonary disease':ab,ti OR Asthma/exp OR Asthma:ab,ti 3. 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti 4. 1-3 AND Guidelines, systematic reviews, retrieved with the above searches, and used as source for individual studies: Holland, 2012 Prem, 2013 Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	08 July 2015
In/Exclusion criteria	**Population**: Include: Adults or children with asthma or chronic pulmonary obstructive disease (COPD) **Intervention**: Include: Any type of breathing exercises or breathing retraining. Breathing control exercises of slow and deep breathing, diaphragmatic breathing, pursed lip breathing, relaxation techniques. Exclude: long term interventions (exercise programs lasting several weeks or months) **Comparison**: Include: no intervention or another intervention such as asthma education **Outcome**: Include: Dyspnea or breathlessness, breathing pattern Exclude: long term outcomes such as quality of life, functional exercise capacity **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Holland, 2012, Australia	Systematic review	16 randomized controlled trials with a sample size varying between 21 to 324 participants and mean age ranging from 51 to 73 years.	wide variety of breathing exercises.	
Prem, 2013, India	Systematic review	3 randomized controlled trials including 254 asthma patients	breathing retraining or diaphragmatic breathing vs asthma education	

Synthesis of findings
No studies could be included after examination of the randomized studies.

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	**Systematic reviews** Holland AE, Hill CJ, Jones AY, McDonald CF. *Breathing exercises for chronic obstructive pulmonary disease*. Cochrane Database of Systematic Reviews 2012, Issue 10. Art. No.: CD008250 Prem V, Sahoo RC and Adhikari P. *Effect of diaphragmatic breathing exercise on quality of life in subjects with asthma: A systematic review*. Physiotherapy Theory and Practice 2013, 29(4):271-277

Coughing – Warm humid air (First aid)

Question (PICO)	In humans with a cough (P), does warm humid air (I) compared to dry air (C) help to cough up slimes or to improve health outcomes (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh cough] OR cough*:ti,ab,kw OR phlegm*:ti,ab,kw 2. [mh humidity] OR humid*:ti,ab,kw OR "cool mist":ti,ab,kw OR [mh steam] OR steam:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Cough[Mesh] OR cough*[TIAB] OR phlegm[TIAB] OR phlegms[TIAB] 2. Humidity[Mesh] OR humid*[TIAB] OR "cool mist"[TIAB] OR steam[Mesh] OR steam[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Coughing/exp OR cough*:ab,ti OR phlegm:ab,ti OR phlegms:ab,ti 2. Humidity/exp OR humid*:ab,ti OR 'water vapor'/exp OR steam:ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	7 August 2015
In/Exclusion criteria	**Population**: Adults and children with a cough **Intervention**: Warm humid air. **Outcome** Coughing **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available.

	Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Donnely, 2006, UK	Systematic review	children <18 years with prolonged non-specific cough.	1. ionisers (positive and negative) 2. vaporisers 3. humidifiers 4. air filters 5. regular vacuuming 6. other dust reduction methods	

Synthesis of findings
No studies were included in the systematic review.

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	**Systematic reviews** Donnelly D, Everard M, Chang AB. *Indoor air modification interventions for prolonged non-specific cough in children*. Cochrane Database of Systematic Reviews 2006, Issue 3. Art. No.: CD005075

Coughing – Covering mouth (Prevention)

Question (PICO)	In humans with a cough (P), does covering the mouth during coughing (I) compared to not covering the mouth (C) prevent infection of other people (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh cough] OR cough*:ti,ab,kw 2. (cover*:ti,ab,kw AND mouth:ti,ab,kw) OR etiquette:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Cough[Mesh] OR cough*[TIAB] 2. (cover*[TIAB] AND mouth[TIAB]) OR etiquette[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Coughing/exp OR cough*:ab,ti 2. (Cover*:ab,ti AND mouth:ab,ti) OR etiquette:ab,ti 3. 1-2 AND
Search date	27 July 2015
In/Exclusion criteria	**Population** Include: people with a cough or healthy volunteers. **Intervention** Include: covering the mouth with a hand, arm, sleeve, tissue,…

	Comparison Include: not covering the mouth **Outcome** Include: infection of other people, droplet size, droplet velocity **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Coughing – Risk factors

Question (PICO)	In humans (P), which risk factors (RF) exist resulting in coughing (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh cough] OR cough*:ti,ab,kw 2. [mh "risk factors"] OR risk*:ti,ab,kw 3. [mh humidity] OR humid*:ti,ab,kw OR ventilat*:ti,ab,kw OR heat*:ti,ab,kw 4. 1-3 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Cough[Mesh] OR cough*[TIAB] 2. "Risk factors"[Mesh] OR risk*[TIAB] 3. Humidity[Mesh] OR humid*[TIAB] OR ventilat*[TIAB] OR heat*[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Coughing/exp OR cough*:ab,ti 2. 'risk factor'/exp OR (Risk NEXT/1 factor*):ab,ti 3. Humidity/exp OR humid*:ab,ti OR ventilat*:ab,ti OR heat*:ab,ti 4. 1-3 AND

	Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	11 August 2015
In/Exclusion criteria	**Population** Healthy people or healthy volunteers **Intervention** Include: risk factors resulting in coughing, such as humidity, temperature. Exclude: habitual risk factors such as smoking; dampness, molding damage in buildings **Outcome** Coughing **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Rib fractures – Light pressure on painful spot (First aid)

Question (PICO)	In humans with rib fractures (P), is light pressure on the painful spot (I) compared to no pressure (C) effective and feasible to change functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "rib fractures"] OR "rib fracture*":ti,ab,kw **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Rib fractures"[Mesh] OR "rib fracture"[TIAB] 2. Pressure[Mesh] OR Pressure*[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'rib fracture'/exp OR (rib:ab,ti AND (fracture:ab,ti OR fractures:ab,ti)) 2. Pressure/exp OR pressure*:ab,ti

	3. 1-2 AND
Search date	28 July 2015
In/Exclusion criteria	**Population**: Include: people with rib fractures **Intervention**: Include: light pressure on painful spot **Comparison**: Include: no light pressure on painful spot **Outcome**: Include: pain **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Breath-holding spells – Blowing in the face (First aid)

Question (PICO)	In children with breath-holding spells (P), does blowing in the face (I) compared to not blowing in the face (C) help to stop the breath-holding spell (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "Breath holding"] OR ("breath-holding":ti,ab,kw AND (spell*:ti,ab,kw OR attack*:ti,ab,kw)) **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "breath holding"[Mesh] OR ("breath-holding"[TIAB] AND (spell*[TIAB] OR attack*[TIAB])) 2. Child[Mesh] OR child*[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'breath holding'/exp OR ('breath-holding':ab,ti AND (spell*:ab,ti OR attack*:ab,ti)) 2. Child/exp OR child*:ab,ti 3. 1-2 AND

Search date	27 July 2015
In/Exclusion criteria	**Population** Include: Children with breath-holding spells **Intervention** Include: blowing in the face of the child with breath-holding spells. Exclude: pharmaceutical interventions, such as piracetam, melatonin or iron supplementation. **Comparison** Include: not blowing in the face **Outcome** Include: stopping of the breath holding spell **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Breath-holding spells – Removing child from the situation (First aid)

Question (PICO)	In children with breath-holding spells (P), does removing the child from the situation that created the breath-holding spell (I) compared to not removing the child (C) help to stop the breath-holding spell (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "Breath holding"] OR ("breath-holding":ti,ab,kw AND (spell*:ti,ab,kw OR attack*:ti,ab,kw)) **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "breath holding"[Mesh] OR ("breath-holding"[TIAB] AND (spell*[TIAB] OR attack*[TIAB])) 2. Child[Mesh] OR child*[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'breath holding'/exp OR ('breath-holding':ab,ti AND (spell*:ab,ti OR attack*:ab,ti))

	2. Child/exp OR child*:ab,ti 3. 1-2 AND
Search date	27 July 2015
In/Exclusion criteria	**Population** Include: Children with breath-holding spells **Intervention** Include: blowing in the face of the child with breath-holding spells. Exclude: pharmaceutical interventions, such as piracetam, melatonin or iron supplementation. **Comparison** Include: not blowing in the face **Outcome** Include: stopping of the breath holding spell **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

STOMACH AND BACK

Stomach pain – Posture (First Aid/Prevention)

Question (PICO)	Among persons (P), is a certain posture (I) compared to another posture (C) an effective first aid or preventive intervention for stomach pain (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh gastritis] OR [mh stomach ulcer] OR [mh dyspepsia] OR [mh peptic ulcer hemorrhage] OR [mh stomach rupture] OR [mh gastric emptying] OR Gastritis:ti,ab,kw OR "Stomach ulcer":ti,ab,kw OR Dyspepsia:ti,ab,kw OR ((rupture:ti,ab,kw OR bleeding:ti,ab,kw) AND stomach:ti,ab,kw) OR 'gastric emptying':ti,ab,kw 2. [mh posture] OR posture:ti,ab,kw OR postures:ti,ab,kw 3. 1 AND 2 **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Gastritis[Mesh] OR "Stomach ulcer"[Mesh] OR Dyspepsia[Mesh] OR "Peptic ulcer hemorrhage"[Mesh] OR "Stomach rupture"[Mesh] OR "Gastric emptying"[Mesh] OR Gastritis[TIAB] OR "Stomach ulcer"[TIAB] OR Dyspepsia[TIAB] OR ((rupture[TIAB] OR bleeding[TIAB]) AND stomach[TIAB]) OR "Gastric Emptying"[TIAB] 2. Posture[Mesh] OR postures[tiab] OR posture[tiab] 3. 1 AND 2 4. Gastritis[Mesh] OR Stomach ulcer[Mesh] OR Dyspepsia[Mesh] OR Peptic ulcer hemorrhage[Mesh] OR "Gastric emptying"[Mesh] 5. Posture[Mesh] 6. Time limit: articles until 18/10/2010 (search date HELP 2011) 7. 4-6 AND 8. 3 NOT 7 **Embase** (via Embase.com interface) using the following search strategy: 1. Gastritis/exp OR 'Stomach ulcer'/exp OR 'dyspepsia'/exp OR 'peptic ulcer bleeding'/exp OR 'stomach emptying'/exp OR gastritis:ab,ti OR 'stomach ulcer':ab,ti OR dyspepsia:ab,ti OR ((rupture:ab,ti OR bleeding:ab,ti) AND stomach:ab,ti) OR 'gastric emptying':ab,ti 2. 'body posture'/exp OR posture:ab,ti OR postures:ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	25 August 2015
In/Exclusion criteria	**Population:** Include: healthy people, people with (symptoms of) gastritis, stomach ulcer, dyspepsia, peptic ulcer, reflux. **Intervention:** Include: any body position (during/after consuming a solid/liquid meal) that can be provided by lay people. Exclude: any body position that cannot be provided by lay people. **Comparison:** Include: studies that compare different body positions **Outcome:** Include: Direct disease-related outcomes for gastritis, stomach ulcer, dyspepsia, peptic ulcer and/or reflux. If not present, indirect outcomes related to gastric emptying (e.g. T1/2) were included. Only short-term effects were included (within 24 hours) Exclude: Long-term effects of the intervention

	Study design: Include: a systematic review (of diagnostic accuracy studies) was included if the search strategy and selection criteria are clearly described and if at least MEDLINE and one other relevant database was searched. If no systematic review was published within the last 5 years, a search for individual experimental/observational studies was performed (from 2008-2015). Exclude: case series**,** cross-sectional studies, animal studies, *ex vivo* or *in vitro* studies. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline)

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Doran, 1998, Australia	Experimental: Randomized controlled trial (within subjects design)	8 non-smoking healthy male volunteers, mean age 24 years (range 18–34 years)	Intervention: left lateral decubitus position after eating a large meal (650 g, 1302 kcal) Control: sitting position after eating a large meal (650 g, 1302 kcal)	
Ikeda, 2008, Japan	Experimental: Randomized controlled trial (within subjects design)	10 healthy male volunteers (median age, 28 years old; range, 22-33 years)	Intervention: supine position after drinking a liquid meal (200 mL, 200 kcal) Control: sitting position after drinking a liquid meal (200 mL, 200 kcal)	
Jeske, 2005, Switzerland	Experimental: Randomized controlled trial (within subjects design)	21 healthy subjects (13 women, 8 men; mean age, 31.3±7.8 yr)	Intervention 1: supine and 20° head-up position after drinking 750 mL carbon dioxide and 300 mL orange juice Intervention 2: supine and 20° head-down position after drinking 750 mL carbon dioxide and 300 mL orange juice Control: Supine position after drinking 750 mL carbon dioxide and 300 mL orange juice	
Jones, 2006, Australia	Experimental: Randomized controlled trial (within subjects design)	8 healthy young subjects (five males, three females; mean age, 24.0 ± 2.4 years)	Intervention: lying position after drinking 600 ml water with 75 g glucose Control: sitting position after drinking 600 ml water with 75 g glucose	
Loots, 2013, The Netherlands	Experimental: Randomized controlled trial (within subjects design)	10 patients with gastro-oesophageal reflux disease (seven men, median (range) age: 31 (18–57) years) and 10 healthy controls [four men, median (range) age: 22 (19–57) years	Intervention: 30 min test meal infusion (400 mL, 2048kJ) and 30 min postprandial in right lateral position Control: 30 min test meal infusion (400 mL, 2048kJ) and 30 min	

			postprandial in left lateral position	
Moore, 1988, USA	Experimental: Randomized controlled trial (within subjects design)	8 healthy male volunteer subjects (median age = 32.5 (21-43) years	Intervention 1: lying after eating a 300 g standardized test meal (208 kcal) Intervention 2: standing after eating a 300 g standardized test meal (208 kcal) Intervention 3: combined sitting-standing after eating a 300 g standardized test meal (208 kcal) Control: sitting after eating a 300 g standardized test meal (208 kcal)	
Spiegel, 2000, USA	Experimental: Non-randomized controlled trial (within subjects design)	9 healthy women aged 29.6±5.4 years (range 20–38)	Intervention: eating 300 g of soup (120 kcal) + eating an egg sandwich (307 kcal) immediately/20 minutes later in the supine position Control: eating 300 g of soup (120 kcal) + eating an egg sandwich (307 kcal) immediately/20 minutes later in the sitting position	
Valeur, 2015, Norway	Experimental: Randomized controlled trial (within subjects design)	8 healthy adolescents (4 females and 4 males aged 14 years)	Intervention: right lateral recumbent position while eating a test meal (500 mL soup, 20 kcal) Control: left lateral recumbent position while eating a test meal (500 mL soup, 20 kcal)	
Van Wijk, 2007, Australia	Experimental: Randomized controlled trial (within subjects design)	10 preterm infants (7 males and 3 females) with a median postnatal age of 23 days (range, 11 to 62 days)	Intervention: right lateral position, then breast milk or formula as feeding Control: left lateral position, then breast milk or formula as feeding	
Victor, 1975, United Kingdom	Experimental: Randomized controlled trial (within subjects design)	12 healthy infants (4 term, 4 preterm and 4 small-for-dates who are clinically well)	Intervention 1: prone position Intervention 2: right lateral position Intervention 3: left lateral position Control: supine position	The test meals (10% glucose, 556 mOsm/kg) were given during the first 24 hours of life and all infants were maintained

				in the required position for at least 3 hours before and for 30 minutes after the feed.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Comparator: sitting position				
T ½ (time for emptying of 50% of the meal, in minutes)	Left lateral decubitus vs sitting	Not statistically significant: 202±12 vs 197±10, MD:5 £† (p=0.40)	1, 8 vs 8 (within subjects design) §	Doran, 1998
	Standing vs sitting	Not statistically significant: 70.4±7.7 (mean±SEM) vs 75.8±8.0 MD:-5.4 £† (p>0.05)		Moore, 1988
	Sitting-standing vs sitting	Statistically significant: 57.9±6.6 (mean±SEM) vs 75.8±8.0 MD:-17.9 £† (p=0.01) *In favour of sitting-standing*		
	Supine vs sitting	Statistically significant: 116.9±13.7 (mean±SEM) vs 75.8±8.0, MD:-41.1 £† (p=0.01) *In favour of sitting*	1, 8 vs 8 (within subjects design) §	
	Supine vs sitting	Statistically significant: 107 (91-217) (median and range) vs 89.5 (76-110) MD:17.5 £† (p=0.0125) *In favour of sitting*	1, 10 vs 10 (within subjects design) §	Ikeda, 2008
	Supine vs sitting	Statistically significant: 136±32 vs 103±37 MD:33 £† (p<0.01) *In favour of sitting*	1, 9 vs 9 (within subjects design) §	Spiegel, 2000
Lag phase (time immediately before activity was seen in the proximal small intestine)	Supine vs sitting	Not statistically significant: 2.3±1.4 vs 5.4±1.3 MD:-3.1 £† (p=0.06)	1, 8 vs 8 (within subjects design) §	Jones, 2006
Comparator: supine position				
Total number of refluxes per person	Head-up vs supine	Not statistically significant: 5.0 (1.5-5.5) (median and interquartile range) vs 5.0 (2.0-5.5) MD: 0 £† (p>0.05)	1, 21 vs 21 (within subjects design) §	Jeske, 2005
	Head-down vs supine	Not statistically significant: 5.0 (2.0-6.0) (median and interquartile range) vs 5.0 (2.0-5.5) MD: 0 £† (p>0.05)		
Percentage retention of feeds (in 30 minutes)	Prone vs supine position	Statistically significant: 33.3±2.9 vs 39±2.8 MD: -5.7 £† (p<0.05) *In favour of prone position*	1, 12 vs 12 (within subjects design) §	Victor, 1975
	Right lateral vs supine position	Statistically significant: 33.9±3.8 vs 39.3±3.0 MD: -5.7 £† (p<0.05) *In favour of right lateral position*		

	Left lateral vs supine position	Not statistically significant: 41.1±2.1 vs 40.3±2.9 MD: 0.8 £† (p>0.05)		
Comparator: left lateral position				
Gastric emptying time (expressed as time to reach peak ^{13}C excretion (time to Tmax))	Right lateral vs left lateral position	Patients with GERD Statistically significant: 36 (26-46) (mean and interquartile range) vs 49 (41-74) MD: -13 £† (p=0.007) *In favour of right lateral position*	1, 10 vs 10 (within subjects design) §	Loots, 2013
		Healthy people Statistically significant: 43 (35-54) (mean and interquartile range) vs 48.5 (43-73) MD: -5.5 £ † (p=0.017) *In favour of right lateral position*		
Gastric emptying (expressed as gastric volume (mL))		After 10 minutes Statistically significant: 292±79 vs 411±50 MD: -119 £ † (p<0.01) *In favour of right lateral position*	1, 8 vs 8 (within subjects design) §	Valeur, 2015
		After 20 minutes Statistically significant: 215±73 vs 340±80 MD: -125 £ † (p<0.05) *In favour of right lateral position*		
T ½ (time for emptying of 50% of the meal, in minutes)		Statistically significant: 37.0±21.1 vs 61.2±24.8 MD: -24.2 £ † (p<0.05) *In favour of right lateral position*	1, 10 vs 10 (within subjects design) §	Van Wijk, 2007

Mean ± SD (unless otherwise indicated)
£ No CI (of the effect size) available
† Imprecision (lack of data)
§ Imprecision (limited sample size)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Doran, 1998	Randomised, allocation concealment unclear	Unclear	No	No	within subjects design
Ikeda, 2008	Randomised, allocation concealment unclear	Unclear	No	No	within subjects design
Jeske, 2005	Randomised, allocation concealment unclear	Unclear	No	No	within subjects design
Jones, 2006	Randomised, allocation concealment unclear	Unclear	No	No	within subjects design
Loots, 2013	Randomised, allocation concealment unclear	No	No	No	within subjects design
Moore, 1988	Randomised, allocation concealment unclear	Unclear	No	No	within subjects design
Spiegel, 2000	Not randomised	Unclear	No	No	within subjects design
Valeur, 2015	Randomised, allocation concealment unclear	Unclear	No	No	within subjects design
Van Wijk, 2007	Randomised, allocation concealment unclear	Unclear	No	No	within subjects design

Victor, 1975	Randomised, allocation concealment unclear	Unclear	No	No	within subjects design

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes and lack of data
Inconsistency	0	
Indirectness	-1	Indirect outcome for stomach pain (i.e. gastric emptying)
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	**Comparator: sitting position** There is limited evidence in favour of the sitting position (combined with standing). In making this evidence conclusion, we place a higher value on postures with statistical significant outcomes over postures with non-statistical significant outcomes. It was shown that sitting (combined with standing) resulted in a statistically significant accelerated gastric emptying time, compared to the supine position (Ikeda 2008, Moore 1988 and Spiegel 2000). However, a statistically significant accelerated gastric emptying time, when standing (Moore 1988), left lateral position (Doran 1988) or lying (Jones 2006) compared to sitting, could not be demonstrated. Evidence is of low quality and results cannot be considered precise due to limited sample size and lack of data. **Comparator: supine position** There is limited evidence in favour of the prone and right lateral position. In making this evidence conclusion, we place a higher value on statistical significant outcomes over non-statistical significant outcomes. It was shown that the prone and right lateral position resulted in a statistically significant decreased retention of the feeds, compared to the supine position (Victor 1975). However, a statistically significant decreased retention of the feeds and a decreased number of reflux episodes, when head up/down position (Jeske 2005) or the left lateral position (Victor 1975) compared to the supine position, could not be demonstrated. Evidence is of low quality and results cannot be considered precise due to limited sample size and lack of data. **Comparator: left lateral position** There is limited evidence in favour of the right lateral position. It was shown that the right lateral position resulted in a statistically significant decreased gastric volume and an accelerated gastric emptying time, compared to the left lateral position (Loots 2013, Valeur 2015 and van Wijk 2007). Evidence is of low quality and results cannot be considered precise due to limited sample size and lack of data.
Reference(s)	**Individual studies** Doran S, Jones KL, Andrews JM, Horowitz M. *Effects of meal volume and posture on gastric emptying of solids and appetite*. Am J Physiol. 1998, 275(5 Pt 2):R1712-1718. Ikeda T, Inamori M, Fujisawa N, Iwasaki T, Akiyama T, Akimoto K, Mawatari H, Iida H, Endo H, Nozaki Y, Sakamoto Y, Fujita K, Takahashi H, Yoneda M, Yoneda K, Goto A, Abe Y, Kirikoshi H, Kobayashi N, Kubota K, Saito S, Nakajima A. *Effects of body positions on gastric emptying with enteral nutrition: a crossover study using a continuous real time 13C breath test (BreathID system).* Hepatogastroenterology. 2008, 55(86-87):1905-1907. Jeske HC, Borovicka J, von Goedecke A, Meyenberger C, Heidegger T, Benzer A. *The influence of postural changes on gastroesophageal reflux and barrier pressure in nonfasting individuals*. Anesth Analg. 2005, 101(2):597-600.

	Jones KL, O'Donovan D, Horowitz M, Russo A, Lei Y, Hausken T. *Effects of posture on gastric emptying, transpyloric flow, and hunger after a glucose drink in healthy humans*. Dig Dis Sci. 2006, 51(8):1331-1338. Loots C, Smits M, Omari T, Bennink R, Benninga M, van Wijk M. *Effect of lateral positioning on gastroesophageal reflux (GER) and underlying mechanisms in GER disease (GERD) patients and healthy controls*. Neurogastroenterol Motil. 2013, 25(3):222-229. Moore JG, Datz FL, Christian PE, Greenberg E, Alazraki N. *Effect of body posture on radionuclide measurements of gastric emptying*. Dig Dis Sci. 1988, 33(12):1592-1595. Spiegel TA, Fried H, Hubert CD, Peikin SR, Siegel JA, Zeiger LS. *Effects of posture on gastric emptying and satiety ratings after a nutritive liquid and solid meal*. Am J Physiol Regul Integr Comp Physiol. 2000, 279(2):R684-R694. Valeur J, Berstad A, Hausken T. *The effect of body position on postprandial perceptions, gastric emptying, and intragastric meal distribution: an ultrasonographic study in reclining healthy subjects*. Scand J Gastroenterol. 2015, 50(2):170-173. van Wijk MP, Benninga MA, Dent J, Lontis R, Goodchild L, McCall LM, Haslam R, Davidson GP, Omari T. *Effect of body position changes on postprandial gastroesophageal reflux and gastric emptying in the healthy premature neonate*. J Pediatr. 2007, 151(6):585-590. Victor YH. *Effect of body position on gastric emptying in the neonate*. Arch Dis Child. 1975, 50(7):500-504.

Stomach pain – Eating a spicy meal (First Aid/Prevention)

Question (PICO)	In people with stomach pain (P), is avoiding a spicy meal effective as a prevention or first aid technique (I) for gastritis/stomach ulcer/peptic ulcer bleeding/stomach rupture/dyspepsia (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh gastritis] OR [mh stomach ulcer] OR [mh dyspepsia] OR [mh peptic ulcer hemorrhage] OR [mh stomach rupture] OR [mh gastric emptying] OR Gastritis:ti,ab,kw OR "Stomach ulcer":ti,ab,kw OR Dyspepsia:ti,ab,kw OR ((rupture:ti,ab,kw OR bleeding:ti,ab,kw) AND stomach:ti,ab,kw) OR 'gastric emptying':ti,ab,kw 2. [mh capsicum] OR pepper*:ti,ab,kw OR chilli:ti,ab,kw 3. 1 AND 2 **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Gastritis[Mesh] OR "Stomach ulcer"[Mesh] OR Dyspepsia[Mesh] OR "Peptic ulcer hemorrhage"[Mesh] OR "Stomach rupture"[Mesh] OR "Gastric emptying"[Mesh] OR Gastritis[TIAB] OR "Stomach ulcer"[TIAB] OR Dyspepsia[TIAB] OR ((rupture[TIAB] OR bleeding[TIAB]) AND stomach[TIAB]) OR "Gastric Emptying"[TIAB] 2. Capsicum [Mesh] OR pepper*[TIAB] OR chilli[TIAB] 3. 1 AND 2 4. Gastritis[Mesh] OR Stomach ulcer[Mesh] OR Dyspepsia[Mesh] OR Peptic ulcer hemorrhage[Mesh] OR "Gastric emptying"[Mesh] 5. Beverages[Mesh] OR Fluid therapy[Mesh] OR Food[Mesh] 6. Time limit: articles until 18/10/2010 (search date HELP 2011) 7. 4-6 AND 8. 3 NOT 7 **Embase** (via Embase.com interface) using the following search strategy: 1. Gastritis/exp OR 'Stomach ulcer'/exp OR 'dyspepsia'/exp OR 'peptic ulcer bleeding'/exp OR 'stomach emptying'/exp OR gastritis:ab,ti OR 'stomach ulcer':ab,ti

	OR dyspepsia:ab,ti OR ((rupture:ab,ti OR bleeding:ab,ti) AND stomach:ab,ti) OR 'gastric emptying':ab,ti 2. Pepper/exp OR pepper*:ab,ti OR chilli:ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	17 August 2015
In/Exclusion criteria	**Population:** Include: healthy people, people with (symptoms of) gastritis, stomach ulcer, dyspepsia, peptic ulcer, reflux. **Intervention:** Include: meals containing spicy food (e.g. chili, peppermint oil) Exclude: meals containing no spicy food **Comparison:** Include: no spicy food Exclude: other spicy food, any medication **Outcome:** Include: Direct disease-related outcomes for gastritis, stomach ulcer, dyspepsia, peptic ulcer and/or reflux. If not present, indirect outcomes related to gastric emptying (e.g. T1/2) were included. Only short-term effects were included (within 24 hours) Exclude: Long-term effects of the intervention (e.g. chronic use (5-6 weeks) of chilli powder). **Study design:** Include: a systematic review was included if the search strategy and selection criteria are clearly described and if at least MEDLINE and one other relevant database was searched. If no systematic review was published within the last 5 years, individual experimental and/or observational studies were included. Exclude: case series**,** animal studies, *ex vivo* or *in vitro* studies. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline)

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Horowitz, 1992, Australia	Experimental: Non-randomized controlled trial (within subjects design)	8 normal Caucasian male volunteers, median age 21 years (range: 19-35)	Intervention: chilli powder (20g) added to meal Control: no chilli powder	Meal: 300 g of cooked minced beef, 200 g of baked beans, 100 g of water and 50 radio-opaque plastic markers
Inamori, 2007, Japan	Experimental: Randomized controlled trial (within subjects design)	10 male healthy volunteers (mean age, 25.2 years; median age, 24 years; range, 22–34 years)	Intervention: test meal (200 kcal per 200 ml) containing 0.64 ml of peppermint oil Control: test meal (200 kcal per 200 ml)	
Milke, 2006, Mexico	Experimental: Uncontrolled before-after study (within subjects design)	12 healthy subjects without gastro-oesophageal reflux symptoms before and after ingestion of one of two kinds of chilli	Intervention: ingest 3 g daily of cascabel chilli (*Capsicum annum coraciforme* containing 880 ppm of capsaicin) or ancho chilli (*Capsicum annum grossum* containing 488 ppm of capsaicin)	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
T ½ (time for emptying of 50% of the meal, in minutes)	Chilli powder in meal vs no chilli powder	Statistically significant: 176 (142-330) (median and range) vs 156 (105-215) MD: 16 £ † (p<0.05) *in favour of no chilli powder*	1, 8 vs 8 (within subjects design) §	Horowitz, 1992
	Peppermint oil in meal vs no peppermint oil in meal	Not statistically significant: 114.3 (80.7-133.0) (median and range) vs 114.3 (102.8-138.2) MD: 0 £ † (p=0.11)	1, 10 vs 10 (within subjects design) §	Inamori, 2007
Number of reflux episodes	Before chilli ingestion vs after chilli ingestion	Statistically significant: 33 (4-108) (median and interquartile range) vs 62 (15-175) MD: 29 £ † (p=0.009) *in favour of no chilli ingestion*	1, 12 vs 12 (within subjects design) §	Milke, 2006
% time with pH <4		Statistically significant: 4 (0-7) (median and interquartile range) vs 8 (1-47) MD: -4 £ † (p=0.011) *in favour of no chilli ingestion*		

Mean ± SD (unless otherwise indicated)
£ No CI (of the effect size) available
† Imprecision (lack of data)
§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Horowitz, 1992	unclear	unclear	no	no	within subjects
Inamori, 2007	unclear	unclear	no	no	within subjects
Milke, 2006	Yes, no control group included	unclear	no	no	Before-after study

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/lack of data
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [D]**	

Conclusion	**Chilli** There is limited evidence in favour of meals containing no chilli (powder). It was shown that meals containing no chilli resulted in a statistically significant decreased gastric emptying time (T1/2), a decreased number of reflux episodes and a reduced time with pH<4, compared to meals containing chilli. (Horowitz 1992, Milke 2006). Evidence is of low quality and results cannot be considered precise due to limited sample size and lack of data. **Peppermint oil** There is limited evidence showing no difference between meals containing peppermint oil and meals containing no peppermint oil. A statistically significant increased gastric emptying time (T1/2) consuming meals containing peppermint oil compared to meals containing no peppermint oil could not be demonstrated (Inamori 2007). Evidence is of low quality and results cannot be considered precise due to limited sample size and lack of data.
Reference(s)	**Individual studies** Horowitz M, Wishart J, Maddox A, Russo A. T*he effect of chilli on gastrointestinal transit*. J Gastroenterol Hepatol. 1992, 7(1):52-56. Inamori M, Akiyama T, Akimoto K, Fujita K, Takahashi H, Yoneda M, Abe Y, Kubota K, Saito S, Ueno N, Nakajima A. *Early effects of peppermint oil on gastric emptying: a crossover study using a continuous real-time 13C breath test (BreathID system)*. J Gastroenterol. 2007, 42(7):539-542. Milke P, Diaz A, Valdovinos MA, Moran S. *Gastroesophageal reflux in healthy subjects induced by two different species of chilli (Capsicum annum)*. Dig Dis. 2006, 24(1-2):184-188.

Stomach pain – Physical activity (First aid/Prevention)

Question (PICO)	Among persons (P), are certain physical activities (I) compared to other/no physical activities (C) an effective first aid or preventive intervention for stomach pain (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh gastritis] OR [mh stomach ulcer] OR [mh dyspepsia] OR [mh peptic ulcer hemorrhage] OR [mh stomach rupture] OR [mh gastric emptying] OR Gastritis:ti,ab,kw OR "Stomach ulcer":ti,ab,kw OR Dyspepsia:ti,ab,kw OR ((rupture:ti,ab,kw OR bleeding:ti,ab,kw) AND stomach:ti,ab,kw) OR 'gastric emptying':ti,ab,kw 2. [mh exercise] OR [mh walking] OR [mh running] OR exercise*:ti,ab,kw OR walk*:ti,ab,kw OR run*:ti,ab,kw 3. 1 AND 2 **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Gastritis[Mesh] OR "Stomach ulcer"[Mesh] OR Dyspepsia[Mesh] OR "Peptic ulcer hemorrhage"[Mesh] OR "Stomach rupture"[Mesh] OR "Gastric emptying"[Mesh] OR Gastritis[TIAB] OR "Stomach ulcer"[TIAB] OR Dyspepsia[TIAB] OR ((rupture[TIAB] OR bleeding[TIAB]) AND stomach[TIAB]) OR "Gastric Emptying"[TIAB] 2. Exercise/physiology[Mesh] OR Walking[Mesh] OR Running[Mesh] OR exercise*[TIAB] OR walk*[TIAB] OR run*[TIAB] 3. 1 AND 2 4. Gastritis[Mesh] OR Stomach ulcer[Mesh] OR Dyspepsia[Mesh] OR Peptic ulcer hemorrhage[Mesh] OR "Gastric emptying"[Mesh] 5. Posture[Mesh]

	6. Time limit: articles until 18/10/2010 (search date HELP 2011) 7. 4-6 AND 8. 3 NOT 7 **Embase** (via Embase.com interface) using the following search strategy: 1. Gastritis/exp OR 'Stomach ulcer'/exp OR 'dyspepsia'/exp OR 'peptic ulcer bleeding'/exp OR 'stomach emptying'/exp OR gastritis:ab,ti OR 'stomach ulcer':ab,ti OR dyspepsia:ab,ti OR ((rupture:ab,ti OR bleeding:ab,ti) AND stomach:ab,ti) OR 'gastric emptying':ab,ti 2. Exercise/exp OR 'Physical activity'/exp OR walking/exp OR running/exp OR exercise*:ab,ti OR walk*:ab,ti OR run*:ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	26 August 2015
In/Exclusion criteria	**Population:** Include: healthy people, people with (symptoms of) gastritis, stomach ulcer, dyspepsia, peptic ulcer, reflux. **Intervention:** Include: certain physical activities. Exclude: same type of exercise but small difference in intensity (e.g. cycling at 65 vs 75% VO_{2max}) **Comparison:** Include: other/no physical activities **Outcome:** Include: Direct disease-related outcomes for gastritis, stomach ulcer, dyspepsia, peptic ulcer and/or reflux. If not present, indirect outcomes related to gastric emptying (e.g. T1/2) were included. Only short-term effects were included (within 24 hours) Exclude: Long-term effects of the intervention **Study design:** Include: a systematic review (of diagnostic accuracy studies) was included if the search strategy and selection criteria are clearly described and if at least MEDLINE and one other relevant database was searched. If no systematic review was published within the last 5 years, a search for individual experimental/observational studies was performed (from 2008-2015). Exclude: case series**,** cross-sectional studies, animal studies, *ex vivo* or *in vitro* studies. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year:** Include: All years.

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Franke, 2008, Germany	Experimental: Randomized controlled trial (within subjects design)	10 healthy male volunteers (age 26.2±0.8 yr)	Intervention 1: walking (4.0 km/h on a treadmill) after drinking water (40 mL, 0 kcal) Control: drinking water (40mL, 0 kcal) without walking	The test solutions were given after a 576 kcal meal
Horner, 2015, Australia	Experimental: Not-randomized controlled trial	44 healthy males: 22 active (age 26.5 (23.0-36.3)), 22 inactive (age 27.5 (24.0-34.3))	Intervention: standardised (1676 kJ) pancake meal in the active group Control: standardised (1676 kJ) pancake meal in the inactive group	Participants in the active group reported taking part in various types of physical activity including aerobic exercise, resistance training, field sports and

				combinations of different modes of exercise
Moore, 1990, USA	Experimental: Randomized controlled trial (within subjects design)	10 healthy young (median age = 27 (22-44) years) male subjects	Intervention 1: walking at 3.2 km/hr (treadmill) after eating a 300 g test meal (208 kcal) Intervention 2: walking at 6.4 km/hr (treadmill) after eating a 300 g test meal (208 kcal) Control: standing ad rest after eating a 300 g test meal (208 kcal)	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
T ½ (time for emptying of 50% of the meal, in minutes)	Walking (4.0 km/hr) vs no walking	Statistically significant: 107±5 vs 123±5 MD:-16 £ † (p=0.02) *In favour of walking*	1, 10 vs 10 (within subjects design) §	Franke, 2008
	Active vs inactive	Statistically significant: 157±18 vs 179±21 MD:-22, 95%CI [-34.12;-9.88] (p=0.0004) *In favour of active group*	1, 22 vs 22 §	Horner, 2015
	Walking (3.2 km/hr) vs no walking	Statistically significant: 44.5±3.9 vs 72.6±7.6 MD:-28.1 £ † (p=0.0051) *In favour of walking*	1, 10 vs 10 (within subjects design) §	Moore, 1990
	Walking (6.4 km/hr) vs no walking	Statistically significant: 32±2 vs 72.6±7.6 MD:-40.6 £ † (p=0.0051) *In favour of walking*		

Mean ± SD £ No CI (of the effect size) available
† Imprecision (lack of data)
§ Imprecision (limited sample size)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Franke, 2008, Germany	Randomized, allocation concealment unclear	Unclear	No	No	within subjects design
Horner, 2015, Australia	Not randomized, allocation concealment unclear	Unclear	No	No	
Moore, 1990, USA	Randomized, allocation concealment unclear	Unclear	No	No	within subjects design

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes and lack of data
Inconsistency	0	
Indirectness	-1	Indirect outcome for stomach pain (i.e. gastric emptying)
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is limited evidence in favour of being active (e.g. walking) after having a meal. It was shown that physical activity resulted in a statistically significant accelerated gastric emptying time, compared to no physical activity (Franke 2008, Horner 2015 and Moore 1990). Evidence is of low quality and results cannot be considered precise due to limited sample size and lack of data.
Reference(s)	**Individual studies** Franke A, Harder H, Orth AK, Zitzmann S, Singer MV. *Postprandial walking but not consumption of alcoholic digestifs or espresso accelerates gastric emptying in healthy volunteers*. J Gastrointestin Liver Dis. 2008, 17(1):27-31. Horner KM, Byrne NM, Cleghorn GJ, King NA. *Influence of habitual physical activity on gastric emptying in healthy males and relationships with body composition and energy expenditure*. Br J Nutr. 2015:1-8. Moore JG, Datz FL, Christian PE. *Exercise increases solid meal gastric emptying rates in men.* Dig Dis Sci. 1990, 35(4):428-432.

Stomach pain – Drinking coffee (First Aid/Prevention)

Question (PICO)	In people (P), is drinking coffee (I) effective as a prevention or first aid technique (I) for stomach pain (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh gastritis] OR [mh stomach ulcer] OR [mh dyspepsia] OR [mh peptic ulcer hemorrhage] OR [mh stomach rupture] OR [mh gastric emptying] OR Gastritis:ti,ab,kw OR "Stomach ulcer":ti,ab,kw OR Dyspepsia:ti,ab,kw OR ((rupture:ti,ab,kw OR bleeding:ti,ab,kw) AND stomach:ti,ab,kw) OR 'gastric emptying':ti,ab,kw 2. [mh coffee] OR coffee:ti,ab,kw 3. 1 AND 2 **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Gastritis[Mesh] OR "Stomach ulcer"[Mesh] OR Dyspepsia[Mesh] OR "Peptic ulcer hemorrhage"[Mesh] OR "Stomach rupture"[Mesh] OR "Gastric emptying"[Mesh] OR Gastritis[TIAB] OR "Stomach ulcer"[TIAB] OR Dyspepsia[TIAB] OR ((rupture[TIAB] OR bleeding[TIAB]) AND stomach[TIAB]) OR "Gastric Emptying"[TIAB] 2. Coffee[Mesh] OR coffee[TIAB] 3. 1 AND 2 4. Gastritis[Mesh] OR Stomach ulcer[Mesh] OR Dyspepsia[Mesh] OR Peptic ulcer hemorrhage[Mesh] OR "Gastric emptying"[Mesh] 5. Beverages[Mesh] OR Fluid therapy[Mesh] OR Food[Mesh] 6. Time limit: articles until 18/10/2010 (search date HELP 2011) 7. 7. 4-6 AND 8. 3 NOT 7

	Embase (via Embase.com interface) using the following search strategy: 1. Gastritis/exp OR 'Stomach ulcer'/exp OR 'dyspepsia'/exp OR 'peptic ulcer bleeding'/exp OR 'stomach emptying'/exp OR gastritis:ab,ti OR 'stomach ulcer':ab,ti OR dyspepsia:ab,ti OR ((rupture:ab,ti OR bleeding:ab,ti) AND stomach:ab,ti) OR 'gastric emptying':ab,ti 2. Coffee/exp OR coffee:ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	21 August 2015
In/Exclusion criteria	**Population:** Include: healthy people, people with (symptoms of) gastritis, stomach ulcer, dyspepsia, peptic ulcer, reflux. **Intervention:** Include: Drinking coffee (before, during and/or after meal) **Comparison:** Include: not drinking coffee (water or nothing) (before, during and/or after meal) **Outcome:** Include: Direct disease-related outcomes for gastritis, stomach ulcer, dyspepsia, peptic ulcer and/or reflux. If not present, indirect outcomes related to gastric emptying (e.g. T1/2) were included. Only short-term effects were included (within 24 hours) Exclude: Long-term effects of the intervention **Study design:** Include: a systematic review was included if the search strategy and selection criteria are clearly described and if at least MEDLINE and one other relevant database was searched. If no systematic review was published within the last 5 years, individual experimental and/or observational studies were included. Exclude: case series**,** animal studies, *ex vivo* or *in vitro* studies. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year:** Include: All years.

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Akimoto, 2009, Japan	Experimental: Randomized controlled trial (within subjects design)	6 asymptomatic non-smoking male volunteers	Intervention: Drinking coffee (190 mL black coffee) after a test meal (200 kcal per 200 mL) Control: Not drinking (coffee) after a test meal (200 kcal per 200 mL)	
Boekema, 2000, The Netherlands	Experimental: Randomized controlled trial (within subjects design)	12 healthy male volunteers (mean age 23.4, range 20-28 years)	Intervention: Drinking coffee (280 mL) 10 minutes after which a liquid nutrient meal was ingested together with lactulose. Control: Drinking water (240 mL warm water + 42 mL saline solution (0·9%)) 10 minutes after which a liquid nutrient meal was ingested together with lactulose.	
Chang, 1995, China	Experimental: Non-randomized controlled trial (within subjects design)	21 patients (14 males, 7 females; ages: 29-77 years old) with non-ulcer dyspepsia	Intervention: 500 ml 5% of glucose water and 4g of instant coffee Control: 500 ml 5% of glucose water	

Franke, 2008, Germany	Experimental: Randomized controlled trial (within subjects design)	10 healthy male volunteers (age 26.2±0.8 yr)	Intervention : Espresso (40 mL,0 kcal) Control: water (40 mL,0 kcal)	The test solutions were given after a 576 kcal meal
Lien, 1995, China	Experimental: Non-randomized controlled trial (within subjects design)	93 subjects (56 males, 37 females; mean age 40 years, range 17-77 years) diagnosed as having non-ulcer dyspepsia	Intervention: drink 500 ml of 5% glucose water containing 4 g of regular instant coffee Control: drink 500 ml of 5% glucose water	
Schubert, 2014, Australia	Experimental: Randomized controlled trial (within subjects design)	12 healthy volunteers (9 females, 3 males, age 26.3±6.3 yr)	Intervention 1: decaffeinated coffee with placebo capsules (225 mL) Intervention 2: decaffeinated coffee with caffeine capsules (225 mL) Control: water with placebo capsules (225 mL)	The test solutions were given during and 2 hours after a standard breakfast (pancakes, butter and jam, providing 1676 kJ, 48 g CHO, 17 g FAT, 15 g PRO)

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Drinking coffee before meal				
T ½ (time for emptying of 50% of the meal, in minutes)	Coffee vs no coffee	Not statistically significant: 75.7 (56-157.6) (median and range) vs 83.4 (64.6-148.4) MD:-7.7 £† (p>0.05)	1, 12 vs 12 (within subjects design) §	Boekema, 2000
Drinking coffee after meal				
T ½ (time for emptying of 50% of the meal, in minutes)	Coffee vs no coffee	Statistically significant: 105.7 (85.7-123.1) (median and range) vs 121.5 (107.2-134.0) MD:-15.8 £† (p=0.0277) *in favour of drinking coffee*	1, 6 vs 6 (within subjects design) §	Akimoto, 2009
	Espresso vs water	Not statistically significant: 125±9 vs 123±5 MD:2 £† (p>0.05)	1, 10 vs 10 (within subjects design) §	Franke, 2008
Drinking coffee during meal				
T ½ (time for emptying of 50% of the meal, in minutes)	Coffee versus no coffee	Statistically significant: 35.7±10.5 vs 45.0±23.1 MD:-9.3 £† (p<0.001) *In favour of coffee*	1, 93 vs 93 (within subjects design) §	Lien, 1995
Gastric emptying time		Not statistically significant: No raw data available £† (p=0.1250)	1, 21 vs 21 (within subjects design) §	Chang, 1995
Drinking coffee during and after meal				
T ½ (time for emptying of 50% of the meal, in minutes)	Decaffeinated coffee versus water	Not statistically significant: 177±25 vs 182±34 MD:-5 £† (p>0.05)	1, 12 vs 12 (within-subjects design) §	Schubert, 2014

	Coffee (caffeine) versus water	Not statistically significant: 179±61 vs 182±34 MD:-3 £† (p>0.05)		

Mean ± SD (unless otherwise indicated)
£ No CI (of the effect size) available
† Imprecision (lack of data)
§ Imprecision (limited sample size)

Drinking coffee before meal:
Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Boekema, 2000	Randomized, allocation concealment unclear	unclear	no	no	within subjects design

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/lack of data
Inconsistency	0	
Indirectness	-1	Indirect outcome for stomach pain (i.e. gastric emptying)
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Drinking coffee after meal:
Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Akimoto, 2009	Randomized, allocation concealment unclear	unclear	no	no	within subjects design
Franke, 2008	Randomized, allocation concealment unclear	unclear	no	no	within subjects design

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/lack of data
Inconsistency	0	
Indirectness	-1	Indirect outcome for stomach pain (i.e. gastric emptying)
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Drinking coffee during meal:
Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Chang, 1995	No randomization	Unclear	no	no	within subjects design
Lien, 1995	Randomized, allocation concealment unclear	unclear	no	no	within subjects design

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Limited sample size/lack of data
Inconsistency	0	
Indirectness	-1	Indirect outcome for stomach pain (i.e. gastric emptying)
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Drinking coffee during/after meal:

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Schubert, 2014	No	No	No	No	within subjects

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/lack of data
Inconsistency	0	
Indirectness	-1	Indirect outcome for stomach pain (i.e. gastric emptying)
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	**Drinking coffee before meal** There is limited evidence neither in favour of drinking coffee nor drinking water. A statistically significant delayed gastric emptying, when drinking coffee compared to drinking water, could not be demonstrated (Boekema 2000). Evidence is of low quality and results of this study are imprecise due to limited sample size and lack of data. **Drinking coffee after meal** There is limited evidence in favour of drinking coffee. It was shown that drinking coffee resulted in a statistically significant accelerated gastric emptying time, compared to drinking no coffee (Akimoto 2009). However, in another study a statistically significant accelerated gastric emptying time when drinking espresso compared to drinking water could not be demonstrated (Franke 2008). Evidence is of low quality and results cannot be considered precise due to limited sample size and lack of data. **Drinking coffee during meal** There is limited evidence in favour of drinking coffee. In making this evidence conclusion, we place a higher value on the findings of the higher quality study (Lien 1995, randomization, higher sample size) over the lower-quality study (Chang 1995, no randomization, lower sample size). It was shown that drinking coffee resulted in a statistically significant accelerated gastric emptying time, compared to drinking water (Lien 1995). However, one study showed that a statistically significant accelerated gastric emptying time when drinking coffee compared to not drinking coffee, could not be demonstrated (Chang 1995). Evidence is of low quality and results cannot be considered precise due to the limited sample size and lack of data. **Drinking coffee before and after meal**

	There is limited evidence neither in favour of drinking (decaffeinated) coffee nor drinking water. A statistically significant delayed gastric emptying, when drinking (decaffeinated) coffee compared to drinking water, could not be demonstrated (Schubert 2014). Evidence is of low quality and results of this study are imprecise due to limited sample size and lack of data.
Reference(s)	**Individual studies** Akimoto K, Inamori M, Iida H, Endo H, Akiyama T, Ikeda T, Fujita K, Takahashi H, Yoneda M, Goto A, Abe Y, Kobayashi N, Kirikoshi H, Kubota K, Saito S, Nakajima A. *Does postprandial coffee intake enhance gastric emptying?: a crossover study using continuous real time 13C breath test (BreathID system)*. Hepatogastroenterology. 2009, 56(91-92):918-920. Boekema PJ, Lo B, Samsom M, Akkermans LM, Smout AJ. *The effect of coffee on gastric emptying and oro-caecal transit time*. Eur J Clin Invest. 2000, 30(2):129-134. Chang LM, Chen GH, Chang CS, Lien HC, Kao CH. *Effect of coffee on solid-phase gastric emptying in patients with non-ulcer dyspepsia*. Gaoxiong Yi Xue Ke Xue Za Zhi. 1995, 11(8):425-429. Franke A, Harder H, Orth AK, Zitzmann S, Singer MV. *Postprandial walking but not consumption of alcoholic digestifs or espresso accelerates gastric emptying in healthy volunteers*. J Gastrointestin Liver Dis. 2008, 17(1):27-31. Lien HC, Chen GH, Chang CS, Kao CH, Wang SJ. *The effect of coffee on gastric emptying*. Nucl Med Commun. 1995, 16(11):923-926. Schubert MM, Grant G, Horner K, King N, Leveritt M, Sabapathy S, Desbrow B. *Coffee for morning hunger pangs. An examination of coffee and caffeine on appetite, gastric emptying, and energy intake*. Appetite. 2014, 83:317-326.

Stomach pain – Large/high-caloric/high-fat meal (First Aid/ Prevention)

Question (PICO)	In people with stomach pain (P), is avoiding a large, a high-fat or a high-caloric meal (I) effective in the prevention or first aid for gastritis/stomach ulcer/peptic ulcer bleeding/stomach rupture/dyspepsia (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh gastritis] OR [mh stomach ulcer] OR [mh dyspepsia] OR [mh peptic ulcer hemorrhage] OR [mh stomach rupture] OR [mh gastric emptying] OR Gastritis:ti,ab,kw OR "Stomach ulcer":ti,ab,kw OR Dyspepsia:ti,ab,kw OR ((rupture:ti,ab,kw OR bleeding:ti,ab,kw) AND stomach:ti,ab,kw) OR 'gastric emptying':ti,ab,kw 2. "Meal volume":ti,ab,kw OR ((Food/exp OR Food:ti,ab,kw) and fat:ti,ab,kw) 3. 1 AND 2 **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Gastritis[Mesh] OR "Stomach ulcer"[Mesh] OR Dyspepsia[Mesh] OR "Peptic ulcer hemorrhage"[Mesh] OR "Stomach rupture"[Mesh] OR "Gastric emptying"[Mesh] OR Gastritis[TIAB] OR "Stomach ulcer"[TIAB] OR Dyspepsia[TIAB] OR ((rupture[TIAB] OR bleeding[TIAB]) AND stomach[TIAB]) OR "Gastric Emptying"[TIAB] 2. "Meal volume"[TIAB] OR ((Food[Mesh] OR Food[TIAB]) and fat[TIAB]) 3. 1 AND 2 4. Gastritis[Mesh] OR Stomach ulcer[Mesh] OR Dyspepsia[Mesh] OR Peptic ulcer hemorrhage[Mesh] OR "Gastric emptying"[Mesh] 5. Beverages[Mesh] OR Fluid therapy[Mesh] OR Food[Mesh] 6. Time limit: articles until 18/10/2010 (search date HELP 2011) 7. 7. 4-6 AND 8. 3 NOT 7

	Embase (via Embase.com interface) using the following search strategy: 1. Gastritis/exp OR 'Stomach ulcer'/exp OR 'dyspepsia'/exp OR 'peptic ulcer bleeding'/exp OR 'stomach emptying'/exp OR gastritis:ab,ti OR 'stomach ulcer':ab,ti OR dyspepsia:ab,ti OR ((rupture:ab,ti OR bleeding:ab,ti) AND stomach:ab,ti) OR 'gastric emptying':ab,ti 2. 'meal volume':ab,ti OR ((food/exp OR food:ab,ti) AND fat:ab,ti)) 3. Time limit: articles until 18/10/2010 (search date HELP 2011) 4. 1-3 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	17 August 2015
In/Exclusion criteria	**Population:** Include: healthy people, people with (symptoms of) gastritis, stomach ulcer, dyspepsia, peptic ulcer, reflux. **Intervention:** Include: high-caloric, high-fat or large meals **Comparison:** Include: low-caloric, low-fat or small meals **Outcome:** Include: Direct disease-related outcomes for gastritis, stomach ulcer, dyspepsia, peptic ulcer and/or reflux. If not present, indirect outcomes related to gastric emptying (e.g. T1/2) were included. Only short-term effects were included (within 24 hours) Exclude: Long-term effects of the intervention. **Study design:** Include: a systematic review was included if the search strategy and selection criteria are clearly described and if at least MEDLINE and one other relevant database was searched. If no systematic review was published within the last 5 years, individual experimental and/or observational studies were included. Exclude: case series**,** animal studies, *ex vivo* or *in vitro* studies. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline)

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Doran, 1998, Australia	Experimental: Randomized controlled trial (within subjects design)	8 non-smoking healthy male volunteers, mean age 24 years (range 18–34 years)	Intervention: large meal (650 g, 1302 kcal): 450 g cooked ground beef with in vivo labeled 99mTc-chicken liver and 200 g tomato sauce Control: small meal (217 g, 434 kcal): 150 g ground beef with 99mTc-chicken liver and 67 g sauce.	
French, 1993, United Kingdom	Experimental: Randomized controlled trial (within subjects design)	8 obese volunteers (3 male, 5 female, BMI>30 kg/m^2, age 21-48 years) and 7 age- and sex-matched healthy normal weight subjects (three male, four female, BMI 20-25 kg/m^2, age 22-44 years)	Intervention: High-fat soup (30 g margarine, 317 kcal) Control: Low-fat soup (72 kcal)	
Houghton, 1990, United Kingdom	Experimental: Randomized controlled trial (within subjects design)	7 healthy male volunteers (aged 20-22 years)	Intervention: high fat: 300 ml radiolabeled beef consomme with 60 g (455 kcal) margarine Control: low fat: 300 ml radiolabeled beef consomme	

			without 60 g (455 kcal) margarine	
Jones, 2005, Australia	Experimental: Randomized controlled trial (within subjects design)	10 healthy older subjects (6 men and 4 women) with a mean age of 73.9±1.2 yr (range, 66–80 years)	Intervention: high-volume drink (75 g glucose in 600 mL water, 12.5%) Control: low-volume drink (25 g glucose in 200 mL water, 12.5%)	
Kwiatec, 2009, Switzerland	Experimental: Randomized controlled trial (within subjects design)	16 healthy subjects (9 males and 7 females, age: 20–37 years)	VOLUME Intervention: 800 mL of a multinutrient drink (200 kcal) Control: 200 mL of a multinutrient drink (200 kcal) CALORIES Intervention: 800 mL of a multinutrient drink (400 kcal) Control: 800 mL of a multinutrient drink (200 kcal)	
Moore, 1984, USA	Experimental: Randomized controlled trial (within subjects design)	9 normal males , mean age was 32±2.6 (SEM)	VOLUME Intervention: Large meal (900 g, 208 kcal) Control: Small meal (300 g, 208 kcal) CALORIES Intervention: High-caloric meal (900 g, 633 kcal) Control: Low-caloric meal (900 g, 68 kcal)	
Pehl, 2001, Germany	Experimental: Randomized controlled trial (within subjects design)	12 healthy volunteers (six female, 19-31 years)	Intervention: High-caloric (842 kcal) solid-liquid meal (solid 582 kcal, liquid 260 kcal) Control: Low-caloric (582 kcal) solid-liquid meal	
Peracchi, 2000, Italy	Experimental: Randomized controlled trial (within subjects design)	10 healthy subjects, 5 men and 5 women, aged 21–38 years (mean 28 years)	Intervention: High-caloric meal (550 kcal, carbohydrate 45%, fat 35%, protein 20%) Control: Low-caloric meal (250 kcal, carbohydrate 42%, fat 40%, protein 18%): 1 scrambled egg, butter 10 g, white bread 70 g, lean ham 50 g and orange juice 100 ml plus water 200 ml.	
Stacher, 1990, Austria	Experimental: Randomized controlled trial (within subjects design)	12 healthy male volunteers ranging in age from 23 to 35 years	Intervention: drinking 56 g dairy cream (20 g fat) 20 minutes before a semisolid test meal was taken. Control: drinking 50 mL of water 20 minutes before a semisolid test meal was taken.	The semisolid test meal (1150 kJ) consisted of 250 ml milk,

				15 g sugar, 14 g maize starch and, for flavouring, cinnamon
Wu, 2014, Taiwan	Experimental: Randomized controlled trial (within subjects design)	15 patients (10 female, 5 male; mean 54±10 years old) with gastroesophageal reflux disease	Intervention: high-volume liquid test meal (600 mL, three times (breakfast, lunch, and dinner)) Control: low-volume liquid test meal (300 mL, six times (breakfast, snack, lunch, snack, dinner, and snack))	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
HIGH CALORIC/HIGH FAT MEAL VERSUS LOW CALORIC/LOW FAT MEAL				
T ½ (time for emptying of 50% of the meal, in minutes)	High-fat vs low-fat soup	In obese subjects Statistically significant: 81.1±11.2 vs 50.4±12.2 MD:30.7 £† (p<0.01) *In favour of low-fat soup*	1, 8 vs 8 § (within subjects design)	French, 1993
		In normal-weighted subjects Statistically significant: 86.3±9.2 vs 36.7±2.8 MD:49.6 £† (p<0.01) *In favour of low-fat soup*	1, 7 vs 7 § (within subjects design)	
	High fat meal vs low fat meal	Statistically significant: 88 (49-146) vs 15 (10-57) (median and range) MD:73 £† (p<0.01) *in favour of low fat meal*	1, 7 vs 7 § (within subjects design)	Houghton, 1990
	High-caloric drink vs low-caloric drink	Statistically significant: 74±8 vs 38±8 (mean±SE) MD:36 £† (p<0.05) *In favour of low-caloric drink*	1, 16 vs 16 § (within subjects design)	Kwiatec, 2009
	High-caloric meal vs low-caloric meal	Statistically significant: 288.5 (183-345.5) vs 155.5 (132-194) (median and interquartile range) MD:133 £† (p<0.05) *in favour of low-caloric meal*	1, 12 vs 12 (within subjects design) §	Peracchi, 2000
	Fat-containing drink vs water (before meal)	Statistically significant: 99.2 (53.8-341.1) vs 51 (26.1-206.6) (median and range) MD:48.2 £† (p<0.005) *in favour of water*	1, 12 vs 12 (within subjects design) §	Stacher, 1990
	High-caloric meal vs low-caloric meal	Statistically significant: 153±14 vs 76±10 (mean±SEM) MD:77 £† (p<0.05) *In favour of low-caloric meal*	1, 9 vs 9 (within subjects design) §	Moore, 1984
Reflux episodes (n per 3 hours) (median and range)	High-caloric meal vs low-caloric meal	Not statistically significant: 12 (3-22) vs 12 (3-30) MD:0 £† (p>0.05)	1, 12 vs 12 (within subjects design) §	Pehl, 2001

Reflux duration (minutes) (median and range)		Not statistically significant: 0.4 (0.1-2.8) vs 0.5 (0.1-2.7) (median and range) MD:-0.1 £† (p>0.05)		
% time with pH <4 (median and range)		Not statistically significant: 2.3 (0.2-23.7) vs 3.3 (0.5-17.8) MD:-1 £† (p>0.05)		
LARGE MEAL VERSUS SMALL MEAL				
T ½ (time for emptying of 50% of the meal, in minutes)	Large meal vs small meal	Statistically significant: 197±10 vs 121±19 MD:76 £† (p<0.05) *in favour of small meal*	1, 8 vs 8 (within subjects design) §	Doran, 1998
	Large meal vs small meal	Statistically significant: 144±58 vs 104±17 (mean±SEM) MD:40 £† (p<0.05) *In favour of small meal*	1, 9 vs 9 (within subjects design) §	Moore, 1984
	High volume drink vs low volume drink	Statistically significant: 38±8 vs 56±7 (mean±SE) MD:-18 £† (p=0.03) *In favour of high volume drink*	1, 16 vs 16 (within subjects design) §	Kwiatec, 2009
Gastric emptying (% retention)	High-volume drink vs low-volume drink	Not statistically significant: £† (figure is available, data could not be extracted) (p>0.05)	1, 10 vs 10 (within subjects design) §	Jones, 2005
Symptoms (24h)	High-volume liquid meal vs low-volume liquid meal	Not statistically significant: 18±5 vs 10±5 MD:8 £† (p=0.444)	1, 15 vs 15 (within subjects design) §	Wu, 2014
Total reflux time (%)		Statistically significant: 12.5±5.9 vs 5.5±3.6 MD:7 £† (p=0.045) *In favour of low-volume liquid meal*		
Number of reflux episodes		Not statistically significant: 18±6 vs 13±5 MD:5 £† (p=0.171)		

Mean ± SD (unless otherwise indicated)
£ No CI (of the effect size) available
† Imprecision (lack of data)
§ Imprecision (limited sample size)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
HIGH CALORIC/HIGH FAT MEAL VERSUS LOW CALORIC/LOW FAT MEAL					
Carbonel, 1994	Randomization and allocation concealment unclear	Unclear	No	No	within subjects design
French, 1993	Randomization and allocation concealment unclear	Unclear	No	No	within subjects design
Houghton, 1990	Randomized, allocation concealment unclear	Unclear	No	No	within subjects design
Kwiatec, 2009	Randomized, allocation concealment unclear	No	No	No	within subjects design
Moore, 1984	Randomized, allocation concealment unclear	Unclear	No	No	within subjects design
Pehl, 2001	Randomized, allocation concealment unclear	No	No	No	within subjects design

Peracchi, 2000	Randomized, allocation concealment unclear	Unclear	No	No	within subjects design
Stacher, 1990	Randomized, allocation concealment unclear	No	No	No	within subjects design
LARGE MEAL VERSUS SMALL MEAL					
Doran, 1998	Randomized, allocation concealment unclear	Unclear	No	No	within subjects design
Jones, 2005	Randomized, allocation concealment unclear	No	No	No	within subjects design
Moore, 1984	Randomized, allocation concealment unclear	Unclear	No	No	within subjects design
Kwiatec, 2009	Randomized, allocation concealment unclear	No	No	No	within subjects design
Wu, 2014	Randomized, allocation concealment unclear	No	No	No	within subjects design

Level of evidence

High caloric/high fat meal versus low caloric/low fat meal

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes and lack of data
Inconsistency	0	
Indirectness	-1	Indirect population (healthy volunteers)
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Large meal versus small meal

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes and lack of data
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	**HIGH CALORIC/HIGH FAT MEAL VERSUS LOW CALORIC/LOW FAT MEAL** There is limited evidence in favour of a low-caloric or low-fat meal. In making this evidence conclusion, we place a higher value on statistical significant outcomes over non-statistical significant outcomes. It was shown that a low-caloric or low-fat meal resulted in a statistically significant decreased gastric emptying time, compared to a high-caloric or high-fat meal (French 1993, Houghton 1990, Kwiatec 2009, Moore 1984, Peracchi 2000, Stacher 1990). A statistically significant increased number of reflux episodes, reflux duration or reduced intragastric pH, having a high-caloric meal compared to a low-caloric meal, could not be demonstrated (Pehl 2001). Evidence is of very low quality and results cannot be considered precise due to limited sample sizes and lack of data. **LARGE MEAL VERSUS SMALL MEAL** There is limited evidence in favour of a small meal. In making this evidence conclusion, we place a higher value on the statistical significant outcomes (in majority of the studies) over non-statistical significant outcomes or the statistical significant outcomes in favour of a high-volume drink (Kwiatec 2009). The latter is indicative for "conflicting evidence", however, in the discussion of this paper the following statement is made: "The present findings are consistent with observations from the nutritional sciences where satiation was shown to be related to the meal

	volume (or weight) and calorie density together (i.e., calorie load) rather than either of these variables alone." It was shown that having a small meal resulted in a statistically significant decreased gastric emptying time and a reduced total reflux time, compared to having a large meal (Doran 1998, Jones 2005, Moore 1984, Wu 2014). A statistically significant increased number of reflux episodes, symptoms or gastric retention rate, having a large meal compared to a small meal, could not be demonstrated (Wu 2014). It was shown in one study that a large meal resulted in a statistically significant decreased gastric emptying time (Kwiatec 2009). Evidence is of low quality and results cannot be considered precise due to limited sample size and lack of data.
Reference(s)	**Individual studies** Doran S, Jones KL, Andrews JM, Horowitz M. *Effects of meal volume and posture on gastric emptying of solids and appetite.* Am J Physiol. 1998, 275(5):1712-1718. French SJ, Murray B, Rumsey RD, Sepple CP, Read NW. *Preliminary studies on the gastrointestinal responses to fatty meals in obese people*. Int J Obes Relat Metab Disord. 1993, 17(5):295-300. Houghton LA, Mangnall YF, Read NW. *Effect of incorporating fat into a liquid test meal on the relation between intragastric distribution and gastric emptying in human volunteers*. Gut. 1990, 31(11):1226-1229. Jones KL, O'Donovan D, Russo A, Meyer JH, Stevens JE, Lei Y, Keogh J, Tonkin A, Horowitz M. *Effects of drink volume and glucose load on gastric emptying and postprandial blood pressure in healthy older subjects*. Am J Physiol Gastrointest Liver Physiol. 2005, 289(2):240-248. Kwiatek MA, Menne D, Steingoetter A, Goetze O, Forras-Kaufman Z, Kaufman E, Fruehauf H, Boesiger P, Fried M, Schwizer W, Fox MR. *Effect of meal volume and calorie load on postprandial gastric function and emptying: studies under physiological conditions by combined fiber-optic pressure measurement and MRI.* Am J Physiol Gastrointest Liver Physiol. 2009, 297(5):894-901. Moore JG, Christian PE, Brown JA, Brophy C, Datz F, Taylor A, Alazraki N. *Influence of meal weight and caloric content on gastric emptying of meals in man*. Dig Dis Sci. 1984, 29(6):513-519. Pehl C, Pfeiffer A, Waizenhoefer A, Wendl B, Schepp W. *Effect of caloric density of a meal on lower oesophageal sphincter motility and gastro-oesophageal reflux in healthy subjects*. Aliment Pharmacol Ther. 2001, 15(2):233-239. Peracchi M, Gebbia C, Ogliari C, Fraquelli M, Viganò R, Baldassarri A, Bianchi PA, Conte D. *Influence of caloric intake on gastric emptying of solids assessed by 13C-octanoic acid breath test*. Scand J Gastroenterol. 2000, 35(8):814-818. Stacher G, Bergmann H, Gaupmann G, Schneider C, Kugi A, Höbart J, Binder A, Mittelbach-Steiner G. *Fat preload delays gastric emptying: reversal by cisapride*. Br J Clin Pharmacol. 1990, 30(6):839-845. Wu KL, Rayner CK, Chuah SK, Chiu YC, Chiu KW, Hu TH, Chiu CT. *Effect of liquid meals with different volumes on gastroesophageal reflux disease*. J Gastroenterol Hepatol. 2014, 29(3):469-473.

Stomach pain – Chewing during eating or using chewing gum (Prevention)

Question (PICO)	In people with stomach pain (P), is chewing (I) compared to no chewing (C) effective as prevention for stomach pain (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh gastritis] OR [mh stomach ulcer] OR [mh dyspepsia] OR [mh peptic ulcer hemorrhage] OR [mh stomach rupture] OR [mh gastric emptying] OR Gastritis:ti,ab,kw

	OR "Stomach ulcer":ti,ab,kw OR Dyspepsia:ti,ab,kw OR ((rupture:ti,ab,kw OR bleeding:ti,ab,kw) AND stomach:ti,ab,kw) OR 'gastric emptying':ti,ab,kw 2. Chew*:ti,ab,kw 3. 1 AND 2 **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Gastritis[Mesh] OR "Stomach ulcer"[Mesh] OR Dyspepsia[Mesh] OR "Peptic ulcer hemorrhage"[Mesh] OR "Stomach rupture"[Mesh] OR "Gastric emptying"[Mesh] OR Gastritis[TIAB] OR "Stomach ulcer"[TIAB] OR Dyspepsia[TIAB] OR ((rupture[TIAB] OR bleeding[TIAB]) AND stomach[TIAB]) OR "Gastric Emptying"[TIAB] 2. Chew*[TIAB] 3. 1 AND 2 4. Gastritis[Mesh] OR Stomach ulcer[Mesh] OR Dyspepsia[Mesh] OR Peptic ulcer hemorrhage[Mesh] OR "Gastric emptying"[Mesh] 5. Beverages[Mesh] OR Fluid therapy[Mesh] OR Food[Mesh] 6. Time limit: articles until 18/10/2010 (search date HELP 2011) 7. 4-6 AND 8. 3 NOT 7 **Embase** (via Embase.com interface) using the following search strategy: 1. Gastritis/exp OR 'Stomach ulcer'/exp OR 'dyspepsia'/exp OR 'peptic ulcer bleeding'/exp OR 'stomach emptying'/exp OR gastritis:ab,ti OR 'stomach ulcer':ab,ti OR dyspepsia:ab,ti OR ((rupture:ab,ti OR bleeding:ab,ti) AND stomach:ab,ti) OR 'gastric emptying':ab,ti 2. Chew*:ab,ti 3. 1 AND 2 Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	12 August 2015
In/Exclusion criteria	**Population:** Include: healthy people, people with (symptoms of) gastritis, stomach ulcer, dyspepsia, peptic ulcer, reflux. **Intervention:** Include: Chewing (at a higher frequency) when eating or using chewing gum after eating **Comparison:** Include: Chewing (at a lower frequency) when eating or not using chewing gum after eating **Outcome:** Include: Direct disease-related outcomes for gastritis, stomach ulcer, dyspepsia, peptic ulcer and/or reflux. If not present, indirect outcomes related to gastric emptying (e.g. T1/2) were included. Only short-term effects were included (within 24 hours) Exclude: Long-term effects of the intervention **Study design:** Include: a systematic review was included if the search strategy and selection criteria are clearly described and if at least MEDLINE and one other relevant database was searched. If no systematic review was published within the last 5 years, individual experimental and/or observational studies were included. Exclude: case series**,** animal studies, *ex vivo* or *in vitro* studies. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year:** Include: All years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Moazzez, 2005, United Kingdom	Experimental: Randomized controlled trial	31 subjects presenting with symptoms of reflux (mean age, 49±11.2	Intervention: a refluxogenic meal + chewing gum for half an hour after eating the meal	

	(within subjects design)	years, 19 males, 12 females)	Control: a refluxogenic meal + no chewing gum for half an hour after eating the meal	
Pera, 2002, Italy	Experimental: Randomized controlled trial (within subjects design)	12 healthy non-smoking dental students, nine men and three women, with ages ranging from 18 to 35 yrs	Intervention: chewing a standard meal at 50 masticatory cycles Control: chewing a standard meal at 25 masticatory cycles (only egg/crackers)	The meal (250 kcal) consisted of one egg cooked with butter (10 g), ham (21 g) cut into 5-mm cubes, crackers (25 g), and 500 mL of water
Sakamoto, 2011, Japan	Experimental: Randomized controlled trial (within subjects design)	10 healthy male subjects (mean age, 22; median age, 22; range, 20-28 years)	Intervention: chewing gum (Xylish, 2-3/1 tablet) for an hour following intake of a test meal (200 kcal/200 mL) Control: no chewing gum, test meal only.	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Chewing gum before meal				
T ½ (time for emptying of 50% of the meal, in minutes)	Chewing gum versus no chewing gum	Not statistically significant: 109.26 (92.62-134.25) (median and range) vs 111.82 (89.45-133.98), MD:-2,56 £ † (p=0.575)	1, 10 vs 10 (within subjects design) §	Sakamoto, 2011
Chewing gum after meal				
Number of reflux episodes	Chewing gum versus no chewing gum	Statistically significant: 1 (0-2) (median and interquartile range) vs 2 (1-4), MD:-1 £ † (p<0.01) *in favour of chewing gum*	1, 31 vs 31 (within subjects design) §	Moazzez, 2005
% time with pH <4		Statistically significant: 3.6 (0.3-7.3) (median and interquartile range) vs 5.7 (1.7-13.5), MD:-2.1 £ † (p=0.001) *in favour of chewing gum*		
Chewing frequency during meal				
T ½ (time for emptying of 50% of the meal, in minutes)	Chewing meal at a higher rate versus chewing at a lower rate	Statistically significant: 49.1 (36.5-61.6) (mean and 95%CI) vs 62.5 (49.3-75.7), MD:-13.4 £ † (p<0.01) *in favour of chewing at a higher rate*	1, 12 vs 12 (within subjects design) §	Pera, 2002

£ No CI (of the effect size) available

† Imprecision (lack of data)

§ Imprecision (limited sample size)

Chewing gum before meal:

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Sakamoto, 2011	Randomized, allocation concealment unclear	Unclear	No	No	within subjects design

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/lack of data
Inconsistency	0	
Indirectness	-1	Indirect outcome for stomach pain (i.e. gastric emptying)
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Chewing gum after meal:

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Moazzez, 2005	Randomized, allocation concealment unclear	Unclear	No	No	within subjects design

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Limited sample size
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Moderate [B]**	

Chewing frequency during meal:

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Pera, 2002	Randomized, allocation concealment unclear	No	No	No	within subjects design

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Limited sample size
Inconsistency	0	
Indirectness	-1	Indirect outcome for stomach pain (i.e. gastric emptying)
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	**Chewing gum before meal** There is limited evidence neither in favour of chewing gum nor no chewing gum. A statistically significant delayed gastric emptying time, using chewing gum compared to no chewing gum, could not be demonstrated (Sakamoto 2011). Evidence is of low quality and results of this study are imprecise due to limited sample size and lack of data. **Chewing gum after meal** There is limited evidence in favour of chewing gum. It was shown that chewing gum resulted in a statistically significant decreased number of reflux episodes and a decreased time of pH<4, compared to no chewing gum (Moazzez 2005). Evidence is of moderate quality and results cannot be considered precise due to limited sample size and lack of data. **Chewing frequency during meal** There is limited evidence in favour of chewing food at a higher frequency. It was shown that chewing food at a higher frequency resulted in a statistically significant delayed gastric emptying time, compared to chewing food at a lower frequency (Pera 2002). Evidence is of low quality and results cannot be considered precise due to limited sample size and lack of data.
Reference(s)	**Individual studies** Moazzez R, Bartlett D, Anggiansah A. *The effect of chewing sugar-free gum on gastro-esophageal reflux*. J Dent Res. 2005, 84(11):1062-1065 Pera P, Bucca C, Borro P, Bernocco C, De LA, Carossa S. *Influence of mastication on gastric emptying*. J Dent Res. 2002, 81(3):179-181 Sakamoto Y, Kato S, Sekino Y, Sakai E, Uchiyama T, Iida H, Hosono K, Endo H, Fujita K, Koide T, Takahashi H, Yoneda M, Tokoro C, Goto A, Abe Y, Kobayashi N, Kubota K, Maeda S, Nakajima A, Inamori M. *Change of gastric emptying with chewing gum: evaluation using a continuous real-time C breath test (BreathID system).* J Neurogastroenterol Motil. 2011, 17(2):174-179

Stomach pain – Drinking alcohol (Prevention)

Question (PICO)	In people (P), is drinking alcohol before, during or after meal (I) effective as prevention for stomach pain (O)?
Search Strategy	Database **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh gastritis] OR [mh stomach ulcer] OR [mh dyspepsia] OR [mh peptic ulcer hemorrhage] OR [mh stomach rupture] OR [mh gastric emptying] OR Gastritis:ti,ab,kw OR "Stomach ulcer":ti,ab,kw OR Dyspepsia:ti,ab,kw OR ((rupture:ti,ab,kw OR bleeding:ti,ab,kw) AND stomach:ti,ab,kw) OR 'gastric emptying':ti,ab,kw 2. [mh cacao] OR [mh onions] OR chocolate:ti,ab,kw OR "citrus fruit":ti,ab,kw OR "citrus fruits":ti,ab,kw OR onions:ti,ab,kw OR "butter milk":ti,ab,kw OR buttermilk:ti,ab,kw 3. 1 AND 2 **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Gastritis[Mesh] OR "Stomach ulcer"[Mesh] OR Dyspepsia[Mesh] OR "Peptic ulcer hemorrhage"[Mesh] OR "Stomach rupture"[Mesh] OR "Gastric emptying"[Mesh] OR Gastritis[TIAB] OR "Stomach ulcer"[TIAB] OR Dyspepsia[TIAB] OR ((rupture[TIAB] OR bleeding[TIAB]) AND stomach[TIAB]) OR "Gastric Emptying"[TIAB]

	2. Ethanol[Mesh] OR alcohol[TIAB] 3. 1 AND 2 4. Gastritis[Mesh] OR Stomach ulcer[Mesh] OR Dyspepsia[Mesh] OR Peptic ulcer hemorrhage[Mesh] OR "Gastric emptying"[Mesh] 5. Beverages[Mesh] OR Fluid therapy[Mesh] OR Food[Mesh] 6. Time limit: articles until 18/10/2010 (search date HELP 2011) 7. 7. 4-6 AND 8. 3 NOT 7 **Embase** (via Embase.com interface) using the following search strategy: 1. Gastritis/exp OR 'Stomach ulcer'/exp OR 'dyspepsia'/exp OR 'peptic ulcer bleeding'/exp OR 'stomach emptying'/exp OR gastritis:ab,ti OR 'stomach ulcer':ab,ti OR dyspepsia:ab,ti OR ((rupture:ab,ti OR bleeding:ab,ti) AND stomach:ab,ti) OR 'gastric emptying':ab,ti 2. Alcohol/exp OR alcohol:ab,ti 3. Time limit: articles until 18/10/2010 (search date HELP 2011) 4. 1-3 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	17 August 2015
In/Exclusion criteria	**Population:** Include: healthy people, people with (symptoms of) gastritis, stomach ulcer, dyspepsia, peptic ulcer, reflux. **Intervention:** Include: Drinking alcohol (before, during and/or after meal) **Comparison:** Include: not drinking alcohol (water or nothing) (before, during and/or after meal) **Outcome:** Include: Direct disease-related outcomes for gastritis, stomach ulcer, dyspepsia, peptic ulcer and/or reflux. If not present, indirect outcomes related to gastric emptying (e.g. T1/2) were included. Only short-term effects were included (within 24 hours) Exclude: Long-term effects of the intervention **Study design:** Include: a systematic review was included if the search strategy and selection criteria are clearly described and if at least MEDLINE and one other relevant database was searched. If no systematic review was published within the last 5 years, individual experimental and/or observational studies were included. Exclude: case series**,** animal studies, *ex vivo* or *in vitro* studies. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: All years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Franke, 2005, Germany	Experimental: Randomized controlled trial (within subjects design)	16 healthy male volunteers (aged 29± 2.1 years)	Intervention 1: Ethanol 4% (v/v) (300 mL, 114 kcal) Intervention 2: Ethanol 10% (v/v) (300 mL, 284 kcal) Intervention 3: Beer, 4.8% (v/v) (Eichbaum Pilsener) (300 mL, 223 kcal) Intervention 4: Red wine, 11% (v/v) (Italian Medoc) (300 mL, 380 kcal) Control: Water (300 mL, 0 kcal)	The test solutions were given either together with a low caloric (270 kcal, *n* = 8) or a high caloric (740 kcal, *n* = 8) solid meal. Only data from high caloric meal group were reported.

Franke, 2008, Germany	Experimental: Randomized controlled trial (within subjects design)	Ten healthy male volunteers (age 26.2±0.8 yr)	Intervention 1: Brandy (40 mL, 110 kcal) Intervention 2: Herb flavored liqueur (40 mL, 100 kcal) Intervention 3: Williams pear brandy (40 mL, 90 kcal) Intervention 4: Aquavit (each 40 % (v/v) ethanol concentration) (40 mL, 95 kcal) Intervention 5: 40% (v/v) ethanol (40 mL, 90 kcal) Control: water (40 mL,0 kcal)	The test solutions were given after a 576 kcal meal
Inamori, 2009, Japan	Experimental: Randomized controlled trial (within subjects design)	10 male healthy volunteers (mean age 23.9 years, range 20–34 years)	Intervention: drinking an aperitif (umeshu = 14% alcohol, 101 kcal) before a liquid meal (200 kcal/200 mL) Control: no aperitif, only liquid meal (200 kcal/200 mL)	
Mushambi, 1993, United Kingdom	Experimental: Randomized controlled trial (within subjects design)	10 healthy volunteers (31 years (range 27-42 yr))	Intervention: 6 units of alcohol (whisky 150 ml and water 50 ml) 1 hour after a liquid meal (beef consommé soup, 500 mL, 21 kcal) Control: no alcohol after a liquid meal (beef consommé soup, 500 mL, 21 kcal)	
Pfeiffer, 1992, Germany	Experimental: Randomized controlled trial (within subjects design)	12 healthy volunteers (6 women, 6 men) with a mean age of 24 (range 19-28)	Intervention 1: drinking beer (7.0% v/v) in a liquid test meal Intervention 2: drinking white wine (7.5% v/v) Intervention 3: drinking ethanol (7.5% v/v) Control: drinking water	Liquid test meal = 300 ml of a nutrient solution (15% proteins, 55% carbohydrates, 30% lipids, 1 kcal/ml)
Sekime, 2013, Japan	Experimental: Randomized controlled trial (within subjects design)	27 healthy volunteers (10 males and 17 females), 20–23 years of age	Intervention 1: red wine (60 mL) (without meal) Intervention 2: vodka (60 mL) (without meal) Control: mineral water (60 mL) (without meal)	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Alcoholic beverages before meal (aperitif)				
T ½ (time for emptying of 50% of the meal, in minutes)	Alcohol vs no alcohol	Statistically significant: 132 (113-174) (median and interquartile range) vs 112 (92-134) MD:20 £ † (p=0.0069) *In favour of no alcohol*	1, 10 vs 10 (within subjects design) §	Inamori, 2009
Alcoholic beverages during meal				
T ½ (time for emptying of 50% of the meal, in minutes)	Ethanol 4% (v/v) versus no alcohol (water)	Statistically significant: 158.8±9.3 vs 131.3±7 MD:27.5 £ † (p<0.05) *In favour of no alcohol*	1, 8 vs 8 (within subjects design) §	Franke, 2005
	Ethanol 10% (v/v) versus no alcohol (water)	Statistically significant: 165.6±6.2 vs 131.3±7 MD:34.3 £ † (p<0.05) *In favour of no alcohol (water)*		
	Beer 4.8% (v/v) versus no alcohol (water)	Statistically significant: 163.1±11 vs 131.3±7 MD:31.8 £ † (p<0.05) *In favour of no alcohol (water)*		
	Red wine 11% (v/v) versus no alcohol (water)	Statistically significant: 186.3±8.4 vs 131.3±7 MD:55 £ † (p<0.05) *In favour of no alcohol*		
Intragastric pH (75 minutes after test meal)	Beer versus no alcohol (water)	Statistically significant: 2.6 (2.1-4.5) (median and range) vs 4.4 (1.5-5.7) MD:-1.8 £ † (p<0.05) *In favour of no alcohol*	1, 12 vs 12 (within subjects design) §	Pfeiffer, 1992
	White wine versus no alcohol (water)	Statistically significant: 3.0 (1.8-4.3) (median and range) vs 4.4 (1.5-5.7) MD:-1.4 £ † (p<0.05) *In favour of no alcohol*		
	Ethanol versus no alcohol (water)	Not statistically significant: 4.1 (2.5-6.0) (median and range) vs 4.4 (1.5-5.7) MD:-1.4 £ † (p<0.05)		
Alcoholic beverages after meal (digestif)				
T ½ (time for emptying of 50% of the meal, in minutes)	Brandy versus no alcohol (water)	Not statistically significant: 119±9 vs 123±5 MD:-4 £ † (p>0.05)	1, 10 vs 10 (within subjects design) §	Franke, 2008
	Flavored herb liquor versus no alcohol (water)	Not statistically significant: 123±10 vs 123±5 MD:0 £ † (p>0.05)		
	Williams versus no alcohol (water)	Not statistically significant: 126±6 vs 123±5 MD:3 £ † (p>0.05)		
	Aquavit versus no alcohol (water)	Not statistically significant: 125±9 vs 123±5 MD:2 £ † (p>0.05)		
	40% ethanol versus no alcohol (water)	Not statistically significant: 118±4 vs 123±5 MD:-5 £ † (p>0.05)		

	Alcohol (whisky) versus no alcohol	Statistically significant: 45 (19-90) (median and interquartile range) vs 23 (13-36) MD:22 £ † (p<0.01) *In favour of no alcohol*	1, 10 vs 10 (within subjects design) §	Mushambi, 1993
Alcoholic beverages without meal				
Tlag (the emptying time for 5% of labeled drinks, in minutes)	Red wine versus no alcohol (water)	**Males** Statistically significant: 54.4±2.8 (mean and standard error) vs 36.4±4.3 MD:18 £ † (p<0.05) *In favour of water*	1, 10 vs 10 (within subjects design) §	Sekime, 2013
		Females Not statistically significant: 43.4±1.8 (mean and standard error) vs 38.9±2.2 MD:2.2 £ † (p>0.05)	1, 17 vs 17 (within subjects design) §	
	Vodka versus no alcohol (water)	**Males** Statistically significant: 54.1±4.5 (mean and standard error) vs 36.4±4.3 MD:17.7 £ † (p<0.05) *In favour of water*	1, 10 vs 10 (within subjects design) §	
		Females Not statistically significant: 41.1±1.4 (mean and standard error) vs 38.9±2.2 MD:2.2 £ † (p>0.05)	1, 17 vs 17 (within subjects design) §	

mean ± SD (unless otherwise indicated)
£ No CI (of the effect size) available
† Imprecision (lack of data)
§ Imprecision (limited sample size or low number of events)

Alcohol beverages before meal:

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Inamori, 2009	Randomized, allocation concealment unclear	unclear	no	no	within subjects design

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Limited sample size and lack of data
Inconsistency	0	
Indirectness	-1	Indirect outcome for stomach pain (i.e. gastric emptying)
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Alcohol beverages during meal:

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Franke, 2005	Randomized, allocation concealment unclear	unclear	no	no	within subjects design
Pfeiffer, 1992	Randomized, allocation concealment unclear	unclear	no	no	within subjects design

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Limited sample size and lack of data
Inconsistency	0	
Indirectness	-1	Indirect outcome for stomach pain (i.e. gastric emptying/intragastric pH)
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Alcohol beverages after meal:

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Franke, 2008	Randomized, allocation concealment unclear	unclear	no	no	within subjects design
Mushambi, 1993	Randomized, allocation concealment unclear	unclear	no	no	within subjects design

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Limited sample size and lack of data
Inconsistency	0	
Indirectness	-1	Indirect outcome for stomach pain (i.e. gastric emptying)
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Alcohol beverages without meal

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Sekime, 2013	Randomized, allocation concealment unclear	Unclear	No	Yes (only Tlag, no T1/2 as outcome)	Within subjects design

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Limited sample size and lack of data
Inconsistency	0	
Indirectness	-1	Indirect outcome for stomach pain (i.e. gastric emptying)
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	**Alcoholic beverages before meal (aperitif)** There is limited evidence in favour of drinking no alcohol before a meal. It was shown that drinking alcohol resulted in a statistically significant increased gastric emptying time, compared to no alcohol (Inamori 2009). Evidence is of low quality and results cannot be considered precise due to limited sample size and lack of data. **Alcoholic beverages during meal** There is limited evidence in favour of drinking no alcohol (water) during meal. In making this evidence conclusion, we place a higher value on statistical significant outcomes over non-statistical significant outcomes. It was shown that drinking alcohol resulted in a statistically significant accelerated gastric emptying time and a lower intragastric pH, compared to drinking no alcohol water) (Franke 2005, Pfeiffer 1992). In one study, a statistical significant difference in intragastric pH when drinking ethanol, compared to no alcohol (water), could not be demonstrated (Pfeiffer 1992) Evidence is of low quality and results cannot be considered precise due to limited sample size and lack of data. **Alcoholic beverages after meal (digestif)** There is limited evidence in favour of drinking no alcohol (nothing) after meal. In making this evidence conclusion, we place a higher value on statistical significant outcomes (1 study) over non-statistical significant outcomes (1 study). The study quality and sample sizes of the two studies were the same,expert opinion is needed to (eventually) use this favourable evidence into a recommendation. It was shown that drinking alcohol (whisky) resulted in a statistically significant accelerated gastric emptying time, compared to drinking no alcohol (Mushambi 1993). In one study, a statistical significant difference in gastric emptying time when drinking alcohol, compared to no alcohol (water), could not be demonstrated (Franke 2008). Evidence is of low quality and results cannot be considered precise due to limited sample size and lack of data. **Alcoholic beverages without meal** There is limited evidence in favour of drinking no alcohol in males. It was shown that drinking alcohol resulted in a statistically significant accelerated gastric emptying time, compared to drinking no alcohol (water) (Sekime 2013). In the same study, a statistical significant difference in gastric emptying time in females when drinking alcohol, compared to no alcohol (water), could not be demonstrated (Franke 2008). Evidence is of low quality and results cannot be considered precise due to limited sample size and lack of data.
Reference(s)	**Individual studies** Franke A, Nakchbandi IA, Schneider A, Harder H, Singer MV. *The effect of ethanol and alcoholic beverages on gastric emptying of solid meals in humans*. Alcohol Alcohol.2005, 40(3):187-193 Franke A, Harder H, Orth AK, Zitzmann S, Singer MV. *Postprandial Walking but not Consumption of Alcoholic Digestifs or Espresso Accelerates Gastric Emptying in Healthy Volunteers*. J Gastrointestin Liver Dis 2008, 11(1): 27-31.

	Inamori M, Iida H, Endo H, Hosono K, Akiyama T, Yoneda K, Fujita K, Iwasaki T, Takahashi H, Yoneda M, Goto A, Abe Y, Kobayashi N, Kubota K, Nakajima A. *Aperitif effects on gastric emptying: a crossover study using continuous real-time 13C breath test (BreathID System)*. Dig Dis Sci. 2009, 54(4):816-818. Mushambi MC, Bailey SM, Trotter TN, Chadd GD, Rowbotham DJ. Effect of alcohol on gastric emptying in volunteers. Br J Anaesth. 1993, 71(5):674-676. Pfeiffer A, Högl B, Kaess H. Effect of ethanol and commonly ingested alcoholic beverages on gastric emptying and gastrointestinal transit. Clin Investig. 1992, 70(6):487-491.

Stomach pain – Eating in the evening (timing) (Prevention)

Question (PICO)	In people (P), is avoiding eating later in the evening (I) compared to eating earlier in the evening (C) effective as prevention for stomach pain (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh gastritis] OR [mh stomach ulcer] OR [mh dyspepsia] OR [mh peptic ulcer hemorrhage] OR [mh stomach rupture] OR [mh gastric emptying] OR Gastritis:ti,ab,kw OR "Stomach ulcer":ti,ab,kw OR Dyspepsia:ti,ab,kw OR ((rupture:ti,ab,kw OR bleeding:ti,ab,kw) AND stomach:ti,ab,kw) OR 'gastric emptying':ti,ab,kw 2. [mh Food] OR food:ti,ab,kw OR meal:ti,ab,kw 3. Early:ti,ab,kw OR Late:ti,ab,kw 4. 1-3 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Gastritis[Mesh] OR "Stomach ulcer"[Mesh] OR Dyspepsia[Mesh] OR "Peptic ulcer hemorrhage"[Mesh] OR "Stomach rupture"[Mesh] OR "Gastric emptying"[Mesh] OR Gastritis[TIAB] OR "Stomach ulcer"[TIAB] OR Dyspepsia[TIAB] OR ((rupture[TIAB] OR bleeding[TIAB]) AND stomach[TIAB]) OR "Gastric Emptying"[TIAB] 2. Food[Mesh] OR food[TIAB] OR meal[TIAB] 3. Early[TIAB] OR Late[TIAB] 4. 2 AND 3 5. 1 AND 4 6. Gastritis[Mesh] OR Stomach ulcer[Mesh] OR Dyspepsia[Mesh] OR Peptic ulcer hemorrhage[Mesh] OR "Gastric emptying"[Mesh] 7. Beverages[Mesh] OR Fluid therapy[Mesh] OR Food[Mesh] 8. Time limit: articles until 18/10/2010 (search date HELP 2011) 9. 4-6 AND 10. 5 NOT 7 **Embase** (via Embase.com interface) using the following search strategy: 1. Gastritis/exp OR 'Stomach ulcer'/exp OR 'dyspepsia'/exp OR 'peptic ulcer bleeding'/exp OR 'stomach emptying'/exp OR gastritis:ab,ti OR 'stomach ulcer':ab,ti OR dyspepsia:ab,ti OR ((rupture:ab,ti OR bleeding:ab,ti) AND stomach:ab,ti) OR 'gastric emptying':ab,ti 2. Food/exp OR food:ab,ti OR meal:ab,ti 3. Early:ab,ti OR late:ab,ti 4. 2 AND 3 5. 1 AND 4 6. Time limit: articles until 18/10/2010 (search date HELP 2011) 7. 5 AND 6

	Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	12 August 2015
In/Exclusion criteria	**Population:** Include: healthy people, people with (symptoms of) gastritis, stomach ulcer, dyspepsia, peptic ulcer, reflux. **Intervention:** Include: Eating/drinking later in the evening **Comparison:** Include: Eating/drinking earlier in the evening **Outcome:** Include: Direct disease-related outcomes for gastritis, stomach ulcer, dyspepsia, peptic ulcer and/or reflux. If not present, indirect outcomes related to gastric emptying (e.g. T1/2) were included. Only short-term effects were included (within 24 hours) Exclude: Long-term effects of the intervention **Study design:** Include: a systematic review was included if the search strategy and selection criteria are clearly described and if at least MEDLINE and one other relevant database was searched. If no systematic review was published within the last 5 years, individual experimental and/or observational studies were included. Exclude: case series**,** animal studies, *ex vivo* or *in vitro* studies. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline)

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Piesman, 2007, USA	Experimental: Randomized controlled trial (within subjects design)	32 patients with typical reflux symptoms (63% male, mean age 46 (range 24–74))	Intervention: standard meal 2 hours prior to going to bed Control: standard meal 6 hours prior to going to bed	The meals consisted of a McDonaldsTM Big MacTM (560 kcal), medium french fries (350 kcal), and a medium carbonated beverage such as SpriteTM or 7 UPTM (approximately 600 mL). The calorie content of the meal was approximately 900 kcal. The fat content was 45% and the total volume of the meal was approximately 850 mL.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Total number of nocturnal reflux episodes	Late meal versus early meal	Statistically significant: £ MD:4.8±2.3 (p=0.021) *in favour of early meal*	1, 32 vs 32 (within subjects design) §	Piesman, 2007
Supine reflux (%)		Statistically significant: £ MD:5.2±1.6 (p=0.002) *in favour of early meal*		

£ No means and SD available

§ Imprecision (limited sample size)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Piesman, 2007	Randomised, allocation concealment unclear	Yes	No	No	within subjects design

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/lack of data
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is limited evidence in favour of eating earlier prior to going to bed. It was shown that eating earlier (6 hours prior to going to bed) resulted in a statistically significant decreased number of nocturnal/supine reflux, compared to eating later (2 hours prior to going to bed) (Piesman 2007). Evidence is of low quality and results cannot be considered precise due to limited sample size and lack of data.
Reference(s)	**Individual studies** Piesman M, Hwang I, Maydonovitch C, Wong RK. *Nocturnal reflux episodes following the administration of a standardized meal. Does timing matter?* Am J Gastroenterol. 2007, 102(10):2128-2134.

Stomach pain – Eating/drinking citrus fruits, chocolate, onions or buttermilk (Prevention)

Question (PICO)	In people with stomach pain (P), is avoiding citrus fruits, chocolate, onions or buttermilk effective (I) as prevention for gastritis/stomach ulcer/peptic ulcer bleeding/stomach rupture/dyspepsia (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh gastritis] OR [mh stomach ulcer] OR [mh dyspepsia] OR [mh peptic ulcer hemorrhage] OR [mh stomach rupture] OR [mh gastric emptying] OR Gastritis:ti,ab,kw OR "Stomach ulcer":ti,ab,kw OR Dyspepsia:ti,ab,kw OR ((rupture:ti,ab,kw OR bleeding:ti,ab,kw) AND stomach:ti,ab,kw) OR 'gastric emptying':ti,ab,kw 2. [mh Cacao] OR [mh onions] OR ([mh carbohydrates] and meal:ti,ab,kw) OR chocolate:ti,ab,kw OR "citrus fruit":ti,ab,kw OR "citrus fruits":ti,ab,kw OR onions:ti,ab,kw OR "butter milk":ti,ab,kw OR buttermilk:ti,ab,kw OR ((carbohydrat*:ti,ab,kw OR sugar:ti,ab,kw) AND meal:ti,ab,kw) 3. 1 AND 2 **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Gastritis[Mesh] OR "Stomach ulcer"[Mesh] OR Dyspepsia[Mesh] OR "Peptic ulcer hemorrhage"[Mesh] OR "Stomach rupture"[Mesh] OR "Gastric emptying"[Mesh] OR Gastritis[TIAB] OR "Stomach ulcer"[TIAB] OR Dyspepsia[TIAB] OR ((rupture[TIAB] OR bleeding[TIAB]) AND stomach[TIAB]) OR "Gastric Emptying"[TIAB] 2. Cacao[Mesh] OR Onions[Mesh] OR (Carbohydrates[Mesh] and meal[TIAB]) chocolate[TIAB] OR "citrus fruit"[TIAB] OR "citrus fruits"[TIAB] OR "onions"[TIAB] OR "butter milk"[TIAB] OR buttermilk[TIAB] OR ((carbohydrat*[TIAB] OR sugar[TIAB]) AND meal[TIAB]) 3. 1 AND 2 4. Gastritis[Mesh] OR Stomach ulcer[Mesh] OR Dyspepsia[Mesh] OR Peptic ulcer hemorrhage[Mesh] OR "Gastric emptying"[Mesh] 5. Beverages[Mesh] OR Fluid therapy[Mesh] OR Food[Mesh] 6. Time limit: articles until 18/10/2010 (search date HELP 2011)

	7. 4-6 AND 8. 3 NOT 7 **Embase** (via Embase.com interface) using the following search strategy: 1. Gastritis/exp OR 'Stomach ulcer'/exp OR dyspepsia/exp OR 'peptic ulcer bleeding'/exp OR 'stomach emptying'/exp OR gastritis:ab,ti OR 'stomach ulcer':ab,ti OR dyspepsia:ab,ti OR ((rupture:ab,ti OR bleeding:ab,ti) AND stomach:ab,ti) OR 'gastric emptying':ab,ti 2. Cacao/exp OR onion/exp OR (carbohydrate/exp and meal:ab,ti) OR chocolate:ab,ti OR 'citrus fruit':ab,ti OR 'citrus fruits':ab,ti OR onions:ab,ti OR 'butter milk':ab,ti OR buttermilk:ab,ti OR ((carbohydrat*:ab,ti OR sugar:ab,ti) AND meal:ab,ti) 3. Time limit: articles until 18/10/2010 (search date HELP 2011) 4. 1-3 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	20 August 2015
In/Exclusion criteria	**Population:** Include: healthy people, people with (symptoms of) gastritis, stomach ulcer, dyspepsia, peptic ulcer, reflux. **Intervention:** Include: Eating/drinking citrus fruits, chocolate, onions or buttermilk **Comparison:** Include: not eating/drinking citrus fruits, chocolate, onions or buttermilk **Outcome:** Include: Direct disease-related outcomes for gastritis, stomach ulcer, dyspepsia, peptic ulcer and/or reflux. If not present, indirect outcomes related to gastric emptying (e.g. T1/2) were included. Only short-term effects were included (within 24 hours) Exclude: Long-term effects of the intervention. **Study design:** Include: a systematic review was included if the search strategy and selection criteria are clearly described and if at least MEDLINE and one other relevant database was searched. If no systematic review was published within the last 5 years, individual experimental and/or observational studies were included. Exclude: case series**,** animal studies, *ex vivo* or *in vitro* studies. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline)

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Abdominal pain – Posture (First Aid)

Question (PICO)	Among persons with abdominal pain (P), is a certain posture (I) compared to another posture (C) an effective first aid intervention to reduce pain (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy:

	1. [mh abdominal pain] OR [mh intestinal obstruction] OR [mh appendicitis] OR [mh dysmenorrhea] OR "abdominal pain":ti,ab,kw OR "intestinal obstruction":ti,ab,kw OR appendicitis:ti,ab,kw OR dysmenorrhea:ti,ab,kw 2. [mh posture] OR posture:ti,ab,kw OR postures:ti,ab,kw 3. 1 AND 2 **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Abdominal pain"[Mesh] OR "Intestinal obstruction"[Mesh] OR "Appendicitis"[Mesh] OR dysmenorrhea[Mesh] OR "abdominal pain"[TIAB] OR "Intestinal obstruction"[TIAB] OR "Appendicitis"[TIAB] OR dysmenorrhea[TIAB] 2. Posture[Mesh] OR postures[tiab] OR posture[tiab] 3. 1 AND 2 **Embase** (via Embase.com interface) using the following search strategy: 1. 'abdominal pain'/exp OR 'intestine obstruction'/exp OR 'acute appendicitis'/exp OR dysmenorrhea/exp OR 'abdominal pain':ab,ti OR 'intestinal obstruction':ab,ti OR appendicitis:ab,ti OR dysmenorrhea:ab,ti 2. 'body posture'/exp OR posture:ab,ti OR postures:ab,ti 3. 1-2 AND
Search date	27 August 2015
In/Exclusion criteria	**Population:** Include: healthy people, people with (symptoms of abdominal pain due to) intestinal obstruction, dysmenorrhea or appendicitis. **Intervention:** Include: any body position that can be provided by lay people. Exclude: any body position that cannot be provided by lay people. **Comparison:** Include: studies that compare different body positions **Outcome:** Include: Outcomes related to abdominal pain **Study design:** Include: a systematic review (of diagnostic accuracy studies) was included if the search strategy and selection criteria are clearly described and if at least MEDLINE and one other relevant database was searched. If no systematic review was published within the last 5 years, a search for individual experimental/observational studies was performed (from 2008-2015). Exclude: case series**,** cross-sectional studies, animal studies, *ex vivo* or *in vitro* studies. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline)

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Menstruation (dysmenorrhea) – Exercise (First Aid)

Question (PICO)	Among women with dysmenorrhea (P), is exercise (I) compared to no exercise (C) an effective first aid intervention for pain reduction (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy:

	1. [mh menstruation] OR [mh dysmenorrhea] OR menstruation:ti,ab,kw OR dysmenorrhea:ti,ab,kw 2. [mh exercise] OR exercise*:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Menstruation[Mesh] OR Dysmenorrhea[Mesh] OR menstruation[TIAB] OR dysmenorrhea[TIAB] 2. Exercise[Mesh] OR exercise*[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Menstruation/exp OR dysmenorrhea/exp OR menstruation:ab,ti OR dysmenorrhea:ab,ti 2. Exercise/exp OR exercise*:ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in MEDLINE (via PubMed interface).
Search date	30 August 2015
In/Exclusion criteria	**Population:** Include: women with dysmenorrhea. **Intervention:** Include: exercise therapy. **Comparison:** Include: studies that compare exercise therapy with no exercise therapy. **Outcome:** Include: Outcomes related to pain intensity, pain relief, menstrual cramps **Study design:** Include: a systematic review was included if the search strategy and selection criteria are clearly described and if at least MEDLINE and one other relevant database was searched. If no systematic review was published within the last 5 years, a search for individual experimental/observational studies was performed (from 2008-2015). Exclude: case series**,** cross-sectional studies, animal studies, *ex vivo* or *in vitro* studies. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline)

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Azima, 2015, Iran	Experimental: randomized controlled trial	68 female students with primary dysmenorrhea who performed isometric exercises (intervention, n=34, 20.73±1.08 years) or no intervention (control, n=34, 21.08±1.21 years)	Intervention: a protocol (7 stages) of isometric exercises (8 weeks, 5 days/week, 2 sessions/day and 10 times per session) Control: no intervention	
Brown, 2010, New Zealand	(Cochrane) Systematic Review	1 randomized controlled trial comparing exercise (n=18) with no exercise (n=18) in women with dysmenorrhea	Intervention: 12-week walk or jog training programme (70-85% of the heart rate range), 3 days per week, 30 minutes (+15 minutes warm-up/cool-down) per session Control: no exercise	Last-assessed as up-to-date: 24 August 2009
Rezvani, 2013, Iran	Experimental: randomized controlled trial	40 nonathletic girls with primary dysmenorrhea aged 18-25 years which performed aquatic exercises (intervention,	Intervention: Aquatic exercises (3 sessions/week of 60 minutes for 12 weeks between 2 menstruations)	

		n=20, 20.25±2.02 years) or not (control, n=20, 20.50±1.79 years)	Control: no aquatic exercises	
Vaziri, 2015, Iran	Experimental: randomized controlled trial	105 female students who were suffering from primary dysmenorrhea and were divided into aerobic exercise (intervention 1, n=35, 21.10±2.07 years), stretching exercise (intervention 2, n=35, 20.81±1.94 years) or control group (n=35, 20.43±1.83).	Intervention 1: Aerobic exercises (treadmill device for 20 min, 3 times/week for two menstrual cycles) Intervention 2: 10 stretching exercises (abdomen, pelvis, and groin) that were performed 3 days a week for two menstrual cycles Control: no exercise	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Isometric exercises				
Pain intensity (VAS score 0-10) at second month	Isometric exercises vs no exercise	Not statistically significant: 2.60±4.64 vs 1.94±6.94 MD:0.66, 95%CI [-2.15;3.47] ¥* (p=0.64)	1, 34 vs 34 (power analysis)	Azima, 2015
Pain duration (hours) at third month		Not statistically significant: 4.77±5.29 vs 6.03±8.35 MD:-1.26, 95%CI [-4.58;2.06] ¥* (p=0.46)		
Aerobic exercises				
Menstrual pain (Menstrual disorder questionnaire)	Aerobic exercises vs no exercise	Statistically significant: No raw data/CI available (p<0.05) † *In favour of aerobic exercises*	1, 18 vs 18 §	Israel, 1985
Pain intensity (Menstrual Symptom Questionnaire) at first menstrual cycle		Statistically significant: 32.48±5.8 vs 38.11±3.6 MD:-5.63, 95%CI [-7.89;-3.37]* (p<0.00001) *In favour of aerobic exercises*	1, 35 vs 35 (power analysis)	Vaziri, 2015
Pain intensity (Menstrual Symptom Questionnaire) at second menstrual cycle		Statistically significant: 25.38±7.5 vs 36.97±4.3 MD:-11.59, 95%CI [-14.45;-8.73]* (p<0.00001) *In favour of aerobic exercises*		
Pain intensity (VAS score 0-5) at first period of menstruation	Aerobic (aquatic) exercises versus no exercise	Statistically significant: 2.26±0.48 vs 3.11±0.66 MD:-0.85, 95%CI [-1.21;-0.49]* (p<0.00001) *In favour of aquatic exercises*	1, 20 vs 20 §	Rezvani, 2013
Pain intensity (VAS score 0-5) at third period of menstruation		Statistically significant: 1.42±0.64 vs 3.05±0.75 MD:-1.63, 95%CI [-2.06;-1.20]* (p<0.00001) *In favour of aquatic exercises*		
Stretching exercises				
Pain intensity (Menstrual Symptom Questionnaire) at first menstrual cycle	Stretching exercises versus no exercise	Not statistically significant: 37.40±4.6 vs 38.11±3.6 MD:-0.71, 95%CI [-2.65;1.23]* (p=0.47)	1, 35 vs 35 (power analysis)	Vaziri, 2015

Pain intensity (Menstrual Symptom Questionnaire) at second menstrual cycle		Statistically significant: 23.21±6.8 vs 36.97±4.3 MD:-13.76, 95%CI [-16.43;-11.09]* (p<0.00001) *In favour of stretching exercises*		

Mean ± SD (unless otherwise indicated)
* Calculations done by the reviewer(s) using Review Manager software
§ Imprecision (limited sample size)
¥ Imprecision (large variability of results)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Isometric exercises					
Azima, 2015	Randomized, allocation concealment unclear	Yes	No	No	
Aerobic exercises					
Israel, 1985	Randomized, allocation concealment unclear	Yes	No	No	
Rezvani, 2013	Randomized, allocation concealment unclear	Yes	No	No	
Vaziri, 2015	Randomized, allocation concealment unclear	Unclear	No	No	
Stretching exercises					
Vaziri, 2015	Randomized, allocation concealment unclear	Unclear	No	No	

Level of evidence

Isometric exercises

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Large variability in results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Aerobic exercises

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	0	
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Moderate [B]**	

Stretching exercises

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	0	
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Moderate [B]**	

Conclusion	**Isometric exercises** There is evidence showing no difference between performing isometric exercises and no exercise. It was shown that isometric exercises did not result in a statistically significant difference of menstrual pain intensity/duration, compared to no exercise (Azima 2015). Evidence is of low quality and results cannot be considered as precise due to large variability in results. **Aerobic exercises** There is evidence in favour of performing aerobic exercises. It was shown that aerobic exercises resulted in a statistically significant menstrual pain intensity relief, compared to no exercise (Israel 1985, Rezvani 2013, Vaziri 2015). Evidence is of moderate quality. **Stretching exercises** There is evidence in favour of performing stretching exercises. It was shown that stretching exercises resulted in a statistically significant menstrual pain intensity relief in the second menstrual cycle, compared to no exercise (Vaziri 2015). However, this effect could not be demonstrated in the first menstrual cycle. Evidence is of moderate quality.
Reference(s)	**Individual studies** Azima S, Bakhshayesh HR, Kaviani M, Abbasnia K, Sayadi M. *Comparison of the Effect of Massage Therapy and Isometric Exercises on Primary Dysmenorrhea: A Randomized Controlled Clinical Trial*. J Pediatr Adolesc Gynecol. 2015, S1083-3188(15)00033-9. Israel R, Sutton M, O'Brien K. *Effects of aerobic training on primary dysmenorrhoea symptomology in college females*. Journal of the American College of Health 1985,33:241–244. Rezvani S, Taghian F, Valiani M. *The effect of aquatic exercises on primary dysmenorrhoea in nonathlete girls*. Iran J Nurs Midwifery Res. 2013, 18(5):378-383. Vaziri F, Hoseini A, Kamali F, Abdali K, Hadianfard M, Sayadi M. *Comparing the effects of aerobic and stretching exercises on the intensity of primary dysmenorrhea in the students of universities of bushehr*. J Family Reprod Health. 2015, 9(1):23-28.

Menstruation (dysmenorrhea) – Food (First Aid)

Question (PICO)	Among women with dysmenorrhea (P), are certain food products (I) an effective first aid intervention for pain reduction (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh dysmenorrhea] OR dysmenorrh*:ti,ab,kw OR "menstrual pain":ti,ab,kw OR "menstrual pains":ti,ab,kw OR "painful menstruation":ti,ab,kw OR "painful menstruations":ti,ab,kw 2. [mh food] OR food:ti,ab,kw OR meal:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Dysmenorrhea [Mesh] OR dysmenorrh*[TIAB] OR "menstrual pain"[TIAB] OR "menstrual pains"[TIAB] OR "painful menstruation"[TIAB] OR "painful menstruations"[TIAB] 2. Food[Mesh] OR food[TIAB] OR meal[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy:

	1. Dysmenorrhea/exp OR dysmenorrh*:ab,ti OR 'menstrual pain':ab,ti OR 'menstrual pains':ab,ti OR 'painful menstruation':ab,ti OR 'painful menstruations':ab,ti 2. Food/exp OR food:ab,ti OR meal:ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in MEDLINE (via PubMed interface).
Search date	31 August 2015
In/Exclusion criteria	**Population:** Include: women with dysmenorrhea. **Intervention:** Include: specific food products. Exclude: medication (including vitamin supplements) **Comparison:** Include: studies that compare specific (amounts of) food products to no food/placebo or lower amounts of food products **Outcome:** Include: Outcomes related to pain intensity, pain relief, menstrual cramps **Study design:** Include: a systematic review was included if the search strategy and selection criteria are clearly described and if at least MEDLINE and one other relevant database was searched. If no systematic review was published within the last 5 years, a search for individual experimental/observational studies was performed (from 2008-2015). Cross-sectional studies were included if coffee/chocolate/tea/salt/alcohol consumption (requested by First Aid Service) were analysed as a risk factor for dysmenorrhea Exclude: case series**,** cross-sectional studies, animal studies, *ex vivo* or *in vitro* studies. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year:** Include: All years.

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Balbi, 2000, Italy	Observational: case-control study	347 female students (ages between 14 and 21 years): 293 with primary dysmenorrhea (cases) and 54 without pain (controls)	Information on dietary habits was taken via a questionnaire	
Barnard, 2000, USA	Experimental: randomized controlled trial (within-subjects design)	51 women with moderate to severe abdominal pain during menstruation (age 22–48 years) received in a cross-over design a low fat vegetarian diet for 2 menstrual cycles (intervention) followed by 2 cycles with normal diet and a placebo supplement (control)	Intervention: a low fat vegetarian diet (grains, vegetables, legumes, and fruits, with no quantitative restrictions. Animal products, added oils, fried foods, avocados, olives, nuts, nut butters, and seeds were proscribed.) Control: normal diet and a placebo supplement	See table 2 for detailed dietary characteristics
Di Cintio, 1997, Italy	Observational: case-control study	106 women (median age 27 years) with moderate or severe dysmenorrhoea lasting 12 months or more (cases) and 145 women (median age 26 years) without dysmenorrhoea, admitted for routine	Information was collected by trained interviewers using a standard questionnaire on 50 food items (risk factor)	Only the statistical significant food items between cases and controls were extracted.

		gynaecological examination (controls)		
Gagua, 2012, Georgia	Observational: case-control study	431 women: 276 women suffering from painful menstruation (cases, 16.03±1.39 years) and 148 healthy women with no dysmenorrhea and with regular ovulatory cycles (controls, 15.55±0.87 years)	Information on nutrition (sugar intake) was taken by a questionnaire	
Harlow, 1996, USA	Observational: case-control study	165 female students aged 17 to 19 years that had menstrual pain (cases, n=140) or not (controls, n=15)	Alcohol consumed > once/week	
Unsal, 2010, Turkey	Observational: cross-sectional study	729 women (29.47±8.01 years) that were dichotomized as having dysmenorrhea versus no dysmenorrhea	Alcohol/tea/coffee/cola/chocolate consumption	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Menstrual pain duration (days)	Low fat vegetarian meal versus normal diet	Statistically significant: 2.7±1.9 vs 3.6±1.7 MD: -0.9 £ (p<0.05) *In favour of low fat meal*	1, 31 vs 31 (power-analysis)	Barnard, 2000
Dysmenorrhea	Portions of cheese per week	Statistically significant: 3.5 (0-12) vs 3 (0-14) (median and range) MD:0.5 £ (p=0.04) *In favour of less cheese portions*	1, 106 vs 145 §	Di Cintio, 1997
	Portions of eggs per week	Statistically significant: 1 (0-6) vs 1 (0-4) (median and range) MD:0 £ (p=0.01) *In favour of less eggs portions*		
	High sugar intake versus low sugar intake	Statistically significant: 153/276 vs 66/148 § RR: 1.55, 95%CI [1.03;2.31]* (p=0.03) *In favour of low sugar intake*	1, 276 vs 148	Gagua, 2012
	Alcohol use versus no alcohol use	Not statistically significant: 12/276 vs 6/148 § RR: 1.08, 95%CI [0.40;2.93] ¥* (p=0.89)		
	Mean consumption of pasta	Not statistically significant: 6.69±2.57 vs 6.04±2.82 MD:0.65, 95%CI [-0.16;1.46] (p=0.11)	1, 293 vs 54 §	Balbi, 2000
	Mean consumption of meat	Not statistically significant: 4.03±1.79 vs 4.11±1.90 MD:-0.08, 95%CI [-0.63;0.47] (p=0.77)		
	Mean consumption of fruits	Statistically significant: 4.72±4.14 vs 6.54±3.71		

		MD:-1.82, 95%CI [-2.92;-0.72] (p=0.001) *In favour of higher consumption of fruits*		
	Mean consumption of eggs	Statistically significant: 1.34±1.17 vs 2.27±1.11 MD:-0.93, 95%CI [-1.25;-0.61] (p<0.00001) *In favour of higher consumption of eggs*		
	Mean consumption of fish	Statistically significant: 1.59±1.26 vs 2.31±1.52 MD:-0.72, 95%CI [-1.15;-0.29] (p=0.001) *In favour of higher consumption of fish*		
	Mean consumption of wine	Not statistically significant: 0.39±1.28 vs 0.19±0.69 MD:0.20, 95%CI [-0.04;0.44] ¥ (p=0.10)		
	Alcohol consumption versus no alcohol consumption	Not statistically significant: 64/464 vs 25/265 § OR: 1.46 95%CI [0.94;2.26] ¥ (p=0.09)	1, 729	Unsal, 2010
Menstrual cramps	Alcohol >1/week versus alcohol ≤1/week	Not statistically significant: OR: 0.76, 95%CI [0.53;1.09] £¥ (p>0.05)	1, 140 vs 15 §	Harlow, 1996
Severe menstrual pain		Not statistically significant: OR: 1.38, 95%CI [0.84;2.26] £¥ (p>0.05)	1, 130 vs 35 §	
Menstrual pain >2 days		Statistically significant: OR: 1.95, 95%CI [1.25;3.04] £ (p<0.05) In favour of less alcohol consumption		
Dysmenorrhea	Tea consumption versus no tea consumption	Statistically significant: 330/464 vs 209/265, OR: 0.90 95%CI [0.83;0.98] (p=0.02) *In favour of tea consumption*	1, 729	Unsal, 2010
	Coffee consumption versus no coffee consumption	Not statistically significant: 160/464 vs 89/265 § RR: 1.03 95%CI [0.83;1.27] ¥ (p=0.81)*		
	Chocolate consumption versus no chocolate consumption	Statistically significant: 176/464 vs 73/265 § RR: 1.38 95%CI [1.10;1.73] (p=0.006)* *In favour of no chocolate consumption*		
	Cola consumption	Statistically significant: 288/464 vs 139/265 RR: 1.18 95%CI [1.03;1.35] (p=0.01)* *In favour of no cola consumption*		

Mean ± SD (unless otherwise indicated)

* Calculations done by the reviewer(s) using Review Manager software

£ No raw data/CI available

† Imprecision (lack of data)
§ Imprecision (limited sample size or low number of events)
¥ Imprecision (large variability of results)

Quality of evidence: experimental studies

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Barnard, 2000	No	Yes	Yes	No	Within subjects design

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	0	
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Moderate [B]**	

Quality of evidence: observational studies

Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations
Balbi, 2000	No	No	Yes	Unclear	
Di Cintio, 1997	Yes	No	No	Unclear	
Gagua, 2012	No	No	Yes	No	
Harlow, 1996	Yes	Yes	No	No	
Unsal, 2010	No	No	Yes	No	

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample size/low number of events/large variability in results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Very Low [D]**	

Conclusion	**Low fat vegetarian meal versus normal diet** There is evidence in favour of low fat (vegetarian) meal. It was shown that a low fat (vegetarian) meal resulted in a statistically significant decrease of menstrual pain duration, compared to a normal diet (Barnard 2000) Evidence is of moderate quality. **High sugar intake/fish/fruits/cheese/tea consumption**

	There is limited evidence in favour of eating higher amounts of fish/fruits, a lower sugar/cheese intake, avoiding cola/chocolate or drinking tea. It was shown that eating higher amounts of fish/fruits, a lower sugar/cheese intake, avoiding cola/chocolate or tea consumption resulted in a statistically significant lower risk of dysmenorrhea, compared to eating lower amounts of fish/fruits, a higher sugar/cheese intake, cola/chocolate consumption or no tea consumption (Gagua 2012, Balbi 2000, Di Cintio 1997, Unsal 2010). Evidence is of very low quality and results cannot be considered precise due to limited sample size, low number of events or large variability in results. **Eggs** There is conflicting evidence concerning eating higher/lower amounts of eggs. One study showed that eating higher amounts of eggs resulted in a statistically significant lower risk of dysmenorrhea (Di Cintio 1997) whereas one study showed that this resulted in a statistically significant higher risk of dysmenorrhea (Balbi 2000). Evidence is of very low quality and results cannot be considered precise due to limited sample size/low number of events or large variability in results. **Pasta/meat/coffee** There is limited evidence neither in favour of eating lower versus higher amounts of pasta/meat or drinking coffee or not. A statistically significant increased risk of dysmenorrhea when eating higher amounts of pasta/meat or drinking coffee compared to lower amounts of pasta/meat or not drinking coffee, could not be demonstrated (Balbi 2000, Unsal 2010). Evidence is of very low quality and results cannot be considered precise due to limited sample size/low number of events or large variability in results. **Wine/alcohol** There is limited evidence in favour of drinking no alcohol. In making this evidence conclusion, we place a higher value on statistical significant outcomes over non-statistical significant outcomes. It was shown that alcohol consumption (>1/week) resulted in a statistically significant increased menstrual pain duration, compared to less/no alcohol consumption (≤1/week (Harlow 1996). However, in 4 studies, a statistical significant difference in (severe) menstrual pain/cramps when drinking alcohol compared to no alcohol, could not be demonstrated (Harlow 1996, Balbi 2000, Gagua 2012, Unsal 2010) Evidence is of very low quality and results cannot be considered precise due to limited sample size/low number of events or large variability in results.
Reference(s)	**Individual studies** Balbi C, Musone R, Menditto A, Di Prisco L, Cassese E, D'Ajello M, Ambrosio D, Cardone1 A. *Influence of menstrual factors and dietary habits on menstrual pain in adolescence age*. Eur J Obstet Gynecol Reprod Biol. 2000,91(2):143-148. Barnard ND, Scialli AR, Hurlock D, Bertron P. *Diet and sex-hormone binding globulin, dysmenorrhea, and premenstrual symptoms*. Obstet Gynecol. 2000, 95(2):245-250. Di Cintio E, Parazzini F, Tozzi L, Luchini L, Mezzopane R, Marchini M, Fedele L. *Dietary habits, reproductive and menstrual factors and risk of dysmenorrhoea*. Eur J Epidemiol. 1997, 13(8):925-930. Gagua T, Tkeshelashvili B, Gagua D. *Primary dysmenorrhea: prevalence in adolescent population of Tbilisi, Georgia and risk factors*. J Turk Ger Gynecol Assoc. 2012, 13(3):162-168. Harlow SD, Park M. *A longitudinal study of risk factors for the occurrence, duration and severity of menstrual cramps in a cohort of college women*. Br J Obstet Gynaecol. 1996, 103(11):1134-1142. Unsal A, Tozun M, Aslan G, Ayranci U, Alkan G. *Evaluation of dysmenorrhea among women and its impact on quality of life in a region of western Turkey.* Pakistan journal of medical sciences 2010,26(1):142-147.

Menstruation (dysmenorrhea) – Massage (First Aid)

Question (PICO)	Among women with dysmenorrhea (P), is massage (I) an effective first aid intervention for pain reduction (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh menstruation] OR [mh dysmenorrhea] OR menstruation:ti,ab,kw OR dysmenorrhea:ti,ab,kw 2. [mh massage] OR massage*:ti,ab,kw 3. 1 AND 2 **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Menstruation[Mesh] OR Dysmenorrhea[Mesh] OR menstruation[TIAB] OR dysmenorrhea[TIAB] 2. Massage[Mesh] OR massage*[TIAB] 3. 1 AND 2 **Embase** (via Embase.com interface) using the following search strategy: 1. menstruation/exp OR dysmenorrhea/exp OR menstruation:ab,ti OR dysmenorrhea:ab,ti 2. massage/exp OR massage*:ab,ti 3. 1 AND 2 Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	28 August 2015
In/Exclusion criteria	**Population:** Include: women with dysmenorrhea. **Intervention:** Include: massage. **Comparison:** Include: studies that compare massage with no massage. Exclude: placebo massage (with placebo oil/product), combination massage and medication use. **Outcome:** Include: Outcomes related to pain intensity, pain relief, menstrual cramps **Study design:** Include: a systematic review was included if the search strategy and selection criteria are clearly described and if at least MEDLINE and one other relevant database was searched. If no systematic review was published within the last 5 years, a search for individual experimental/observational studies was performed (from 2008-2015). Exclude: case series**,** cross-sectional studies, animal studies, *ex vivo* or *in vitro* studies. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year:** Include: All years.

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Azima, 2015, Iran	Experimental: randomized controlled trial	68 female students with primary dysmenorrhea who received effleurage massage with lavender oil (intervention, n=34, 21.41±0.95 years) or no intervention (control, n=34, 21.08±1.21 years)	Intervention: effleurage massage (2 consecutive cycles) with lavender oil (in supine position, massage of the upper part of symphysis pubis and umbilicus) Control: no intervention	

Han, 2006, South Korea	Experimental: randomized controlled trial	65 female college students who rated their menstrual cramps to be greater than 6 on a 10-point visual analogue scale and received massage with essential oils of lavender, clary sage, and rose, diluted in almond oil (intervention 1, n=25, 20.6±1.27), massage with almond oil only (intervention 2, n=20, mean age 20.9±1.93) or no intervention (control, n=20, mean age 20.5±0.51)	Intervention 1: abdominal aromatherapy massage (15 minutes) with essential oils of lavender, clary sage, and rose, diluted in almond oil (3% concentration) Intervention 2: massage with almond oil only Control: no intervention	Massages were given every day beginning one week before the start of menstruation and continuing until the first day of menstruation The treatment room for abdominal massage was isolated and equipped with beds warmed by heating pads
Kim, 2011, South Korea	Experimental: non-randomized controlled trial	62 female nurses who rated their menstrual pain >5 on a 10-point visual analogue scale and performed self-aromatherapy massage (intervention 1, n=25, mean age 24.8±1.9), self-massage with almond oil only (intervention 2, n=18, mean age 24.9±1.7) or no intervention (control, n=19, mean age 25.0±2.0)	Intervention 1: self-aromatherapy massage of the abdomen for 10 min with essential oils from rose absolute, rose otto, clary sage, rose geranium and ginger that were diluted in almond oil, jojoba oil, and evening primrose oil (3% concentration) Intervention 2: massage with almond oil only Control: no intervention	Both intervention groups performed self-massage twice on the first and second days of menstruation

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Massage				
Pain intensity (VAS score 0-10) at second month	Massage vs no massage	Not statistically significant: 4.26±2.59 vs 1.94±6.94 MD:2.32, 95%CI [-0.17;4.81]* (p=0.07) ¥	1, 34 vs 34 (power analysis)	Azima, 2015
Pain duration (hours) at third month		Not statistically significant: 4.73±3.58 vs 6.03±8.35 MD:-1.30, 95%CI [-4.35;1.75]* (p=0.407)		
Severity of menstrual cramps (first day) (median and interquartile range)		Not statistically significant: 7.00 (6.0-8.0) vs 7.0 (6.0-8.0) MD:0 £† (p>0.05)	1, 20 vs 20 (power analysis)	Han, 2006

Menstrual pain (change after 24 hours)		Not statistically significant: -1.5±2.2 vs -2.2±0.9, MD:0.7 £ † (p>0.05)	1, 15 vs 15 §	Kim, 2011
Aromatherapy massage				
Severity of menstrual cramps (first day)	Aromatherapy massage vs no massage	Statistically significant: 5.0 (3.0-6.0) (median and interquartile range) vs 7.0 (6.0-8.0), MD:-2 £† (p<0.01) *In favour of aromatherapy massage*	1, 25 vs 20 (power analysis)	Han, 2006
Menstrual pain (change after 24 hours)		Statistically significant: -3.7±1.5 vs -2.2±0.9 MD:1.5 £† (p<0.05) *In favour of aromatherapy massage*	1, 25 vs 15 §	Kim, 2011

Mean ± SD (unless otherwise indicated)
* Calculations done by the reviewer(s) using Review Manager software
£ No CI available
† Imprecision (lack of data)
§ Imprecision (limited sample size)
¥ Imprecision (large variability of results)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Massage vs no massage					
Azima, 2015	Randomized, allocation concealment unclear	Yes	No	No	
Han, 2006	No	No	No	No	
Kim, 2011	No randomisation, allocation concealment unclear	Yes	Yes	No	
Aromatherapy massage vs no massage					
Han, 2006	No	No	No	No	
Kim, 2011	No randomisation, allocation concealment unclear	Yes	Yes	No	

Level of evidence

Massage versus no massage

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Large variability in results (Azima 2015), limited sample size (Kim 2011), lack of data (Han 2006 and Kim 2011)
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Aromatherapy massage versus no massage

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample size (Kim 2011), lack of data (Han 2006 and Kim 2011)
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	**Massage vs no massage** There is limited evidence neither in favour of massage nor no massage. A statistically significant reduced pain intensity/duration, using massage compared to no massage, could not be demonstrated (Azima 2015, Han 2006, Kim 2011). Evidence is of low quality and results of these studies are imprecise due to limited sample size, lack of data and/or large variability of results. **Aromatherapy massage vs no massage** There is limited evidence in favour of aromatherapy massage. It was shown that aromatherapy massage resulted in a statistically significant menstrual pain relief, compared to no massage (Han 2006, Kim 2011). Evidence is of low quality and results cannot be considered precise due to limited sample size and lack of data.
Reference(s)	**Individual studies** Azima S, Bakhshayesh HR, Kaviani M, Abbasnia K, Sayadi M. *Comparison of the Effect of Massage Therapy and Isometric Exercises on Primary Dysmenorrhea: A Randomized Controlled Clinical Trial*. J Pediatr Adolesc Gynecol. 2015, S1083-3188(15)00033-9. Han SH, Hur MH, Buckle J, Choi J, Lee MS. *Effect of aromatherapy on symptoms of dysmenorrhea in college students: A randomized placebo-controlled clinical trial*. J Altern Complement Med. 2006, 12(6):535-541. Kim Y.-J., Lee M.S., Yang Y.S., Hur M.-H. *Self-aromatherapy massage of the abdomen for the reduction of menstrual pain and anxiety during menstruation in nurses: A placebo-controlled clinical trial*. **European Journal of Integrative Medicine** 2011, **3:3:**e165-e168.

Menstruation (dysmenorrhea) – Heat application (First Aid)

Question (PICO)	Among women with dysmenorrhea (P), is heat application (I) an effective first aid intervention for pain reduction (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh menstruation] OR [mh dysmenorrhea] OR menstruation:ti,ab,kw OR dysmenorrhea:ti,ab,kw 2. [mh hot temperature] OR heat*:ti,ab,kw OR warm*:ti,ab,kw 3. 1 AND 2 **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Menstruation[Mesh] OR Dysmenorrhea[Mesh] OR menstruation[TIAB] OR dysmenorrhea[TIAB] 2. "Hot temperature"[Mesh] OR heating[Mesh] OR heat*[TIAB] OR warm*[TIAB] 3. 1 AND 2 **Embase** (via Embase.com interface) using the following search strategy: 1. menstruation/exp OR dysmenorrhea/exp OR menstruation:ab,ti OR dysmenorrhea:ab,ti 2. heat/exp OR heating/exp OR heat*:ab,ti OR warm*:ab,ti 3. 1 AND 2 Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	28 August 2015

In/Exclusion criteria	**Population:** Include: women with dysmenorrhea. **Intervention:** Include: heat application that can be performed by lay people. Exclude: heat application in combination with any medication. **Comparison:** Include: studies that compare heat application with no/unheated application **Outcome:** Include: Outcomes related to pain intensity, pain relief **Study design:** Include: a systematic review was included if the search strategy and selection criteria are clearly described and if at least MEDLINE and one other relevant database was searched. If no systematic review was published within the last 5 years, a search for individual experimental/observational studies was performed (from 2008-2015). Exclude: case series**,** cross-sectional studies, animal studies, *ex vivo* or *in vitro* studies. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline)

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Akin, 2001, USA	Experimental: randomized controlled trial	40 women with primary dysmenorrhoea who received a heated patch plus placebo (intervention, n=20, 32.75±6.47 years) or unheated patch plus placebo (control, n=20, 34.00±6.66 years)	Intervention: heated patch plus placebo Control: unheated patch plus placebo	Subjects were asked to wear a kidney bean–shaped ultra-thin medical device (heated or unheated) that adhered to the inside of the underwear on the lower abdominal region for approximately 12 consecutive hours per day for 2 consecutive days.
Potur, 2014, Turkey	Experimental: randomized controlled trial	Female students who had a history of regular menstrual cycles (during the last 6 months) accompanied by moderate to severe pain (ie, score of 5 or more on the visual analog scale (VAS), 66 students received a heat patch (intervention), 66 received no heat patch (control)	Intervention: heat patch (lower abdomen, directly on the skin, adhering to the underwear) applied on the first day of menstruation for 8 hours, during 2 menstrual cycles Control: no heat patch	Only data from first menstrual cycle were extracted

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Mean pain relief during 2 days (score 0-5)	Heated vs unheated patch	Statistically significant: 3.27 vs 1.95 MD:1.32 £ † (p<0.001) *In favour of heated patch*	1, 20 vs 20 §	Akin, 2001

Pain intensity (VAS score 0-10) at the end of treatment	Heated vs no patch	Statistically significant: 1.99±2.42 vs 5.78±2.63 MD:-3.79, 95%CI [-4.65;-2.93]* (p<0.00001) *In favour of heated patch*	1, 66 vs 66 (power analysis)	Potur, 2014

Mean ± SD (unless otherwise indicated)
* Calculations done by the reviewer(s) using Review Manager software
£ No CI available
† Imprecision (lack of data)
§ Imprecision (limited sample size)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Akin, 2001	Randomized, allocation concealment unclear	Unclear	No	No	
Potur, 2014	Randomized, allocation concealment unclear	Unclear	No	No	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	0	
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Moderate [B]**	

Conclusion	There is evidence in favour of heat application. It was shown that using a heat patch resulted in a statistically significant pain relief, compared to an unheated/no patch (Akin 2001, Potur 2014). Evidence is of moderate quality.
Reference(s)	**Individual studies** Akin MD, Weingand KW, Hengehold DA, Goodale MB, Hinkle RT, Smith RP. *Continuous low-level topical heat in the treatment of dysmenorrhea*. Obstet Gynecol. 2001, 97(3):343-349. Potur DC, Kömürcü N. *The effects of local low-dose heat application on dysmenorrhea*. J Pediatr Adolesc Gynecol. 2014, 27(4):216-221.

Vomiting – Posture (First Aid)

Question (PICO)	Among vomiting persons (P), is a certain posture (I) compared to another posture (C) an effective first aid intervention for pain relief (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh vomiting] OR vomit*:ti,ab,kw 2. [mh posture] OR posture:ti,ab,kw OR postures:ti,ab,kw 3. 1 AND 2 **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Vomiting[Mesh] OR vomit*[TIAB] 2. Posture[Mesh] OR postures[TIAB] OR posture[TIAB]

	3. 1 AND 2 **Embase** (via Embase.com interface) using the following search strategy: 1. vomiting/exp OR vomit*:ab,ti 2. 'body posture'/exp OR posture:ab,ti OR postures:ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	01 September 2015
In/Exclusion criteria	**Population:** Include: vomiting people Exclude: people with positional paroxysmal vertigo **Intervention:** Include: any body position that can be provided by lay people. Exclude: any body position that cannot be provided by lay people. **Comparison:** Include: studies that compare different body positions **Outcome:** Include: Outcomes related to vomiting **Study design:** Include: a systematic review (of diagnostic accuracy studies) was included if the search strategy and selection criteria are clearly described and if at least MEDLINE and one other relevant database was searched. If no systematic review was published within the last 5 years, a search for individual experimental/observational studies was performed (from 2008-2015). Exclude: case series**,** cross-sectional studies, animal studies, *ex vivo* or *in vitro* studies. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline)

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Tandberg, 1989, USA	Experimental: randomized controlled trial (within subjects design)	20 normal fasting adult subjects (mean age of 30.4 years (range, 19 to 44 years), 8 males and 12 females) underwent induced emesis in the knee-chest position (intervention) on one day and in the sitting position (control) on another day	Intervention: knee-chest position Control: sitting position Twenty-five 100 microgram tablets of cyanocobaiamin were ingested as a tracer along with 250 ml tap water. Ten minutes after tracer ingestion, 30 mL ipecac syrup and 840 mL tap water were swallowed.	Ipecac is a drug that was once used as a cough syrup and to induce vomiting

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Mean tracer recovery (microgram)	Knee-chest vs sitting position	Not statistically significant: 51.3, 95%CI [39.9;62.7] vs 51.0, 95%CI [40.0;62.0], MD:0.3 £† (p>0.95)	1, 20 vs 20 § (within subjects design)	Tandberg, 1989

Data are expressed as means

£ No CI of effect measure available

† Imprecision (lack of data)

§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Tandberg, 1989	Randomized, allocation concealment unclear	Unclear	No	No	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample size and lack of data
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is limited evidence neither in favour of the knee-chest position nor the sitting position. A statistically significant increased mean tracer recovery, using the knee-chest position compared to the sitting position, could not be demonstrated (Tandberg 1989). Evidence is of low quality and results of this study are imprecise due to limited sample size and lack of data.
Reference(s)	**Articles:** Tandberg D, Murphy LC. The knee-chest position does not improve the efficacy of ipecac-induced emesis. Am J Emerg Med. 1989,7(3):267-270.

Vomiting – Drinking/eating (timing) (First Aid)

Question (PICO)	In vomiting persons (P), is drinking/eating at an early point (I) compared to a later point (C) an effective first aid intervention for health-related outcomes (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh vomiting] OR vomit*:ti,ab,kw 2. [mh drinking] OR [mh eating] OR drink*:ti,ab,kw OR eat*:ti,ab,kw 3. Early:ti,ab,kw OR timing:ti,ab,kw OR late:ti,ab,kw OR delayed:ti,ab,kw 4. 1-3 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Vomiting[Mesh] OR vomit*[TIAB] 2. Drinking[Mesh] OR eating[Mesh] OR drink*[TIAB] OR eat*[TIAB] 3. Early[TIAB] OR timing[TIAB] OR late[TIAB] OR delayed[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Vomiting/exp OR vomit*:ab,ti 2. Drinking/exp OR eating/exp OR drink*:ab,ti OR eat*:ab,ti 3. Early:ab,ti OR timing:ab,ti OR late:ab,ti OR delayed:ab,ti 4. 1-3 AND
Search date	02 September 2015
In/Exclusion criteria	**Population:** Include: vomiting people Exclude: people in surgical settings **Intervention:** Include: eating/drinking at an early time point after vomiting

	Comparison: Include: eating/drinking at a later point in time after vomiting **Outcome:** Include: Direct health-related outcomes **Study design:** Include: a systematic review (of diagnostic accuracy studies) was included if the search strategy and selection criteria are clearly described and if at least MEDLINE and one other relevant database was searched. If no systematic review was published within the last 5 years, a search for individual experimental/observational studies was performed (from 2008-2015). Exclude: case series, cross-sectional studies, animal studies, *ex vivo* or *in vitro* studies. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year:** Include: all years.

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Vomiting – Drinking (volume) (First Aid)

Question (PICO)	In vomiting persons (P), is drinking small volumes (I) compared to larger volumes (C) an effective first aid intervention for health-related outcomes (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh vomiting] OR vomit*:ti,ab,kw 2. [mh drinking] OR drink*:ti,ab,kw 3. Volume*:ti,ab,kw OR amount*:ti,ab,kw OR quantity:ti,ab,kw OR dose*:ti,ab,kw 4. 1-3 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Vomiting[Mesh] OR vomit*[TIAB] 2. Drinking[Mesh] OR drink*[TIAB] 3. Volume*[TIAB] OR amount*[TIAB] OR quantity[TIAB] OR dose*[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Vomiting/exp OR vomit*:ab,ti 2. Drinking/exp OR drink*:ab,ti 3. Volume*:ab,ti OR amount*:ab,ti OR quantity:ab,ti OR dose*:ab,ti 4. 1-3 AND
Search date	02 September 2015
In/Exclusion criteria	**Population:** Include: vomiting people Exclude: people in surgical settings **Intervention:** Include: drinking small volumes of a certain fluid **Comparison:** Include: drinking larger volumes of a certain fluid **Outcome:** Include: Direct health-related outcomes **Study design:** Include: a systematic review (of diagnostic accuracy studies) was included if the search strategy and selection criteria are clearly described and if at least MEDLINE

	and one other relevant database was searched. If no systematic review was published within the last 5 years, a search for individual experimental/observational studies was performed (from 2008-2015). Exclude: case series**,** cross-sectional studies, animal studies, *ex vivo* or *in vitro* studies. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication years**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Diarrhoea – Drinking (First Aid)

Question (PICO)	In humans with diarrhoea (P), is drinking (I) effective to change functional recovery, complications, time to resumption of usual activities, restoration to the pre-exposure condition, time to resolution of symptoms (O)?
Search Strategy	Databases We used the NICE guideline "Diarrhoea and vomiting caused by gastroenteritis" of 2009. In addition we searched for systematic reviews (without limitations in search date). **The Cochrane Library** (systematic reviews) using the following search term: 1. [mh "Diarrhea"] OR diarrhoea:ti,ab,kw OR diarrhea:ti,ab,kw 2. [mh "Water"] OR [mh "Drinking"] OR water:ti,ab,kw OR drinking:ti,ab,kw OR milk:ti,ab,kw OR juice:ti,ab,kw OR soup:ti,ab,kw OR "soft drink":ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for guidelines and systematic reviews using the following search strategy: 1. "Diarrhea"[Mesh] OR diarrhea[TIAB] OR diarrhoea[TIAB] 2. "Water"[Mesh] OR "Drinking"[Mesh] OR water[TIAB] OR drinking[TIAB] OR milk[TIAB] OR juice[TIAB] OR soup[TIAB] OR soft drink[TIAB] 3. ((((((((((Meta-Analysis as Topic[Mesh])) OR ((meta analy*[TIAB]))) OR ((metaanaly*[TIAB]))) OR ((Meta-Analysis[Publication Type]))) OR ((systematic review*[TIAB] OR systematic overview*[TIAB]))) OR ((Review Literature as Topic[Mesh])))) OR ((cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB]))) OR ((reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB]))) OR ((((selection criteria[TIAB] OR data extraction[TIAB])) AND ((Review[PT]))))) NOT ((Comment[PT] OR Letter[PT] OR Editorial[PT] OR animal[Mesh] NOT (animal[Mesh] AND human[Mesh]))) 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy:

	1. 'diarrhea'/exp OR diarrhea:ab,ti OR diarrhoea:ab,ti 2. 'water'/exp OR 'drinking'/exp OR water:ab,ti OR drinking:ab,ti milk:ab,ti OR juice:ab,ti OR soup:ab,ti OR 'soft drink':ab,ti 3. 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti 4. 1-3 AND Guidelines, systematic reviews, retrieved with the above searches, and used as source for individual studies: Carter, 2015
Search date	20 October 2015
In-/Exclusion criteria	**Population**: Include: people with diarrhoea (developing and developed countries); Exclude: neonates **Intervention**: Include: drinking fluids including water, milk, juices, soup, soft drinks, Oral Rehydration Solution/Therapy (ORS/ORT) for the prevention of dehydration; Exclude: ORS/ORT for the management of dehydration (included in another PICO), probiotics, continuation of breast feeding (included in another PICO) **Comparison**: Include: no drinking, delayed drinking, drinking of another fluid **Outcome**: Include: (symptoms of) diarrhoea, dehydration **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study (taking into account confounding variables at the analysis phase), controlled before and after study or controlled interrupted time series, and the data are available. Exclude: observational studies if intervention is already included in experimental studies, animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline)

Characteristics of included studies

Author, year, Country	Study design	Population	Intervention	Remarks
Brown, 1994, United States	Systematic review	29 randomized clinical trials of 2215 patients. All but two studies included only hospitalized patients. The children's ages ranged from 0 to 59 months.	Comparison 1: Lactose-containing vs non-lactose containing nonhuman milk or formulas Comparison 2: Undiluted vs diluted/delayed nonhuman milk or formulas	
Carter, 2015, United States	Systematic review	79 studies, including 76 cross-sectional surveys/longitudinal surveys and 3 case-control studies	Harmful practices in the management of childhood diarrhoea, including restriction of fluids, breast milk and/	This systematic review used a very sensitive search strategy (see Additional file 1 of the review), however none of

			or food intake during diarrhoea episodes, and incorrect use of modern medicines	the included studies fulfilled our selection criteria, because of study design (majority) or intervention.
Faruque, 1992, Bangladesh	Observational: case-control study	Cases (n=285): children aged between 1 and 35 months with acute watery diarrhoea of six days or less, with moderate or severe dehydration (definite decreased skin elasticity and one or more of four signs: sunken eyes, failure to urinate for six hours, sunken anterior fontanel, and rapid and weak pulse) Controls (n=728): children aged between 1 and 35 months with diarrhoea without dehydration	Risk factors (for prevention of dehydration, which is the goal of diarrhoea management): Withdrawal of breast feeding, use of oral rehydration therapy (ORT) at home [only data about ORT were extracted]	Study included in NICE guideline. In the NICE guideline no studies were identified on the effectiveness of different types of oral fluids (other than ORS solution) in the prevention and treatment of dehydration. The lack of available evidence was not surprising, given the ethical difficulties with undertaking an RCT comparing the administration and withholding of oral fluid supplementation. The case-control design required a sample size of 200 in each study group (with α=0.05, power of 90%, and odds ratio of 2). A field tested, structured, interviewer administered questionnaire was used by trained interviewers. A multivariate analysis was performed.

Synthesis of findings

Outcome	Risk factor	Effect Size	#studies, # participants	Reference
Treatment failure rates	Lactose-containing vs non-lactose containing nonhuman milk or formulas	in children with mild diarrhoea: Not statistically significant: RR: 1.0, 95%CI [0.5;1.9] (p=0.68) £†¥	5 (exact number of participants not provided)	Brown, 1994
Stool frequency		(not taking into account severity of diarrhoea): Statistically significant: 4.0±3.2 vs 3.5±2.9 (p=0.004) ££† *In favour of non-lactose containing milk*	4 (exact number of participants not provided)	
Duration of diarrhoea		(not taking into account severity of diarrhoea): Statistically significant: 92±95 vs 88±95 (p=0.001) ££† *In favour of non-lactose containing milk*	9 (exact number of participants not provided)	

Treatment failure rates	Undiluted vs diluted/delayed nonhuman milk or formulas	in children with mild diarrhoea: Not statistically significant: RR: 1.1, 95%CI [0.7;1.6] (p=0.69) £†¥	5 (exact number of participants not provided)	
Stool frequency		(not taking into account severity of diarrhoea): Statistically significant: 7.3±6.3 vs 7.0±6.6 (p=0.046) ££† *In favour of diluted/delayed milk*	6 (exact number of participants not provided)	
Duration of diarrhoea		(not taking into account severity of diarrhoea): Not statistically significant: 72±32 vs 72±40 (p=0.001) ££†	10 (exact number of participants not provided)	
Risk of diarrhoea evolving in dehydration	No use of oral rehydration therapy (ORT) at home vs ORT at home	Statistically significant: OR: 1.57, 95%CI [1.08;2.29] (p=0.019) £ *With harm for no ORT at home*	1, 285 vs 728 (power analysis)	Faruque, 1992

£ No raw data available
££ No effect size and confidence interval available
£££ No raw data/effect size/confidence interval available
§ Imprecision (low number of events)
† Imprecision (lack of data)
¥ Imprecision (large variability of results)

Milk

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See systematic review (Brown 1994)
Imprecision	-1	Lack of data or large variability in results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

ORT

Quality of evidence

Author, Year	**Inappropriate eligibility criteria**	**Inappropriate methods for exposure and outcome variables**	**Not controlled for confounding**	**Incomplete or inadequate follow-up**	**Other limitations**
Faruque, 1992, Bangladesh	Unclear (no information about matching)	No	No (multivariable analysis)	No	

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	0	
Inconsistency	0	
Indirectness	-1	ORT instead of oral fluid
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Conclusion	**Milk** There is limited evidence neither in favour of lactose-containing milk nor non-lactose containing milk, and neither in favour of undiluted milk nor diluted/delayed milk. In making this evidence conclusion, we place a higher value on the outcome "treatment failure rates", where severity of diarrhoea or dehydration, previous treatment failure and type of treatment were taken into account (as reported by the authors). A statistically significant difference in treatment failure rates using lactose-containing milk compared to non-lactose containing milk, could not be demonstrated (Brown 1994). However, it was shown that lactose-containing milk resulted in a statistically significant increased stool frequency, and duration of diarrhoea, compared to non-lactose containing milk (Brown 1994). A statistically significant difference in treatment failure rates, and duration of diarrhoea, using undiluted milk compared to diluted/delayed milk, could not be demonstrated (Brown 1994). However, it was shown that undiluted milk resulted in a statistically significant increased stool frequency compared to diluted or delayed milk (Brown 1994). Evidence is of low quality and results cannot be considered precise due to lack of data or large variability of results. **Oral Rehydration Therapy (ORT) at home** There is limited evidence with benefit for ORT at home. It was shown that no use of ORT at home resulted in a statistically significant increased risk of diarrhoea evolving in dehydration, compared to use of ORT at home (Faruque 1992). Evidence is of very low quality.
Reference(s)	**Articles** Brown KH, Peerson JM, Fontaine O. *Use of nonhuman milks in the dietary management of young children with acute diarrhea: a meta-analysis of clinical trials*. Pediatrics 1994, 93(1):17-27 Faruque AS, Mahalanabis D, Islam A, Hoque SS, Hasnat A. *Breast feeding and oral rehydration at home during diarrhoea to prevent dehydration*. Arch Dis Child 1992 Aug;67(8):1027-9 **Systematic reviews** Carter E, Bryce J, Perin J, Newby H. *Harmful practices in the management of childhood diarrhea in low- and middle-income countries: a systematic review*. BMC Public Health 2015, 15(1):788 **Guidelines** NICE 2009. Diarrhoea and vomiting caused by gastroenteritis.

Diarrhoea – Hand washing (Prevention)

Question (PICO)	In humans (P), is hand washing (I) compared to no intervention (C) effective to prevent diarrhoea (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "hand disinfection"] OR handwash*:ti,ab,kw OR "hand wash*":ti,ab,kw OR "hand cleansing":ti,ab,kw OR "hand hygiene":ti,ab,kw or "hand sterility":ti,ab,kw 2. [mh diarrhea] OR diarrhea:ti,ab,kw OR diarrhoea:ti,ab,kw 3. 1-2 AND

	MEDLINE (via PubMed interface) for systematic reviews, experimental or observational studies using the following search strategy: 5. "hand disinfection"[Mesh] OR Hand wash*[TIAB] OR hand disinfect*[TIAB] OR hand clean*[TIAB] OR hand hygiene[TIAB] 6. Diarrhea[Mesh] OR diarrhea[TIAB] OR diarrhoea[TIAB] 7. 1-2 AND **Embase** (via Embase.com interface) for systematic reviews, experimental or observational studies using the following search strategy: 1. 'hand washing'/exp OR 'hand washing':ab,ti OR 'hand disinfection':ab,ti OR 'hand cleansing':ab,ti OR 'hand hygiene':ab,ti OR 'hand sterility':ab,ti OR 'hand sanitization':ab,ti 2. 'diarrhea'/exp OR 'diarrhoea':ab,ti OR 'diarrhea':ab,ti 3. 1-2 AND 4. 'prevention'/exp OR 'health education'/exp OR 'health behavior'/exp OR 'self examination'/de OR 'preventive medicine'/exp OR 'prevention':lnk OR 'risk factor'/exp 5. 3-4 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	14 January 2016
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Ejemot-Nwadiaro, 2015, Nigeria	Systematic review		Control: no hand washing promotions.	Cochrane systematic review 2015 (last update 27 may 2015).

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Ejemot-Nwadiaro, 2015, Nigeria	Systematic review	Individuals in institutional settings, communities or households. 54006 children in 12 trails in high-income countries. 15303 participants in 9 community-based trials. Trials were conducted in LMICs in Africa, Asia and South America. 148 adults in 1 trial in a high-risk group (AIDS patients). This trial was conducted in the USA.	Intervention: Activities that promote hand washing after defecation or after disposal of children's faeces and before eating, preparing or handling foods. Control: no hand washing promotions.	Cochrane systematic review 2015 (last update 27 may 2015).

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Incidence of diarrhea	High-income countries: Hand washing vs no intervention (child care centres and schools)	Statistically significant: Rate ratio: 0.70, 95%CI [0.58,0.85] (p=0.00021) *In favour of hand washing intervention*	9, 2349 vs 2315	Ejemot-Nwadiaro, 2015
	Low-income countries: Hand washing vs no intervention (child care centres and schools)	Statistically significant: Rate ratio: 0.66, 95%CI [0.43,0.99] (p=0.046) *In favour of hand washing intervention*	2, 21342 vs 24038	
	Focused hand wash only: Hand washing vs no intervention (child care centres and schools)	Not statistically significant: Rate ratio: 0.69, 95%CI [0.43,1.09] ¥ (p=0.11)	2, 522 vs 523	
	Non focused (Multiple hygiene interventions): Hand washing vs no intervention (child care centres and schools)	Statistically significant: Rate ratio: 0.69, 95%CI [0.57,0.84] (p=0.0002) *In favour of hand washing intervention*	9, 23169 vs 25830	
	Community based trials: Hand washing vs no intervention	Statistically significant: Incidence rate ratio: 0.72, 95%CI [0.62,0.83] (p=0.000017) *In favour of hand washing*	8, 8100 vs 6626	
	Community based trials: Hand washing vs no intervention (Focused hand wash only)	Statistically significant: Rate ratio: 0.63, 95%CI [0.52,0.78] (p=0.000014)	5, 6181 vs 4707	

		In favour of hand washing intervention		
	Community based trials: Hand washing vs no intervention (Non focused: Multiple hygiene interventions)	Statistically significant: Rate ratio: 0.81, 95%CI [0.69,0.95] (p=0.01) *In favour of hand washing intervention*	3, 1919 vs 1919	
	Community based trials (soap provided): Hand washing vs no intervention	Statistically significant: Rate ratio: 0.66, 95%CI [0.56,0.78] (p<0.00001) *In favour of hand washing intervention*	6, 6448 vs 4974	
	Community based trials (no soap provided): Hand washing vs no intervention	Not statistically significant: Rate ratio: 0.84, 95%CI [0.67,1.05] ¥ (p=0.13)	2, 1652 vs 1652	
Episodes of diarrhea	Community based trials: hand washing promotion vs no intervention	Statistically significant: MD: -1.68, 95%CI[-1.93;-1.43] (p<0.00001) *In favour of hand washing promotion*	1, 73 vs 75	

¥ Imprecision (large variability of results)
§ Imprecision (limited sample size or low number of events)

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See systematic review (Ejemot-Nwadiaro 2015) Allocation concealment is often unclear, there is often lack of blinding (it is hard to blind washing or not washing hands but outcome assessors could be blinded).
Imprecision	0	
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Moderate [B]**	

Conclusion	There is evidence from 1 systematic review (including 22 experimental studies) in favour of hand washing (Ejemot-Nwadiaro 2015). It was shown that the promotion of hand washing resulted in a statistically significant decrease of diarrhea compared to no intervention (Ejemot-Nwadiaro 2015). Evidence is of moderate quality.
Reference(s)	**Systematic reviews** Ejemot-Nwadiaro RI, Ehiri JE, Meremikwu MM, Critchley JA. *Hand washing for preventing diarrhoea*. Cochrane Database of Systematic Reviews 2015, Issue 9. Art. No.: CD004265

Diarrhoea – Hand sanitizers (Prevention)

Question (PICO)	In humans (P), is the use of hand sanitizers (I) compared to no intervention (C) effective to prevent diarrhoea (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy:

	4. [mh "hand disinfection"] OR [mh "hand sanitizers"] OR "hand cleans*":ti,ab,kw OR "hand hygiene":ti,ab,kw or "hand sterility":ti,ab,kw OR "hand gel*":ti,ab,kw OR "hand sanitiz*":ti,ab,kw 5. [mh diarrhea] OR diarrhea:ti,ab,kw OR diarrhoea:ti,ab,kw OR hepatitis:ti,ab,kw 6. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "hand disinfection"[Mesh] OR "Hand Sanitizers"[Mesh] OR hand disinfect*[TIAB] OR hand cleans*[TIAB] OR hand hygiene[TIAB] OR hand gel*[TIAB] OR hand sanit*[TIAB] 2. Diarrhea[Mesh] OR diarrhea[TIAB] OR diarrhoea[TIAB] OR hepatitis[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 5. 'hand sanitizer'/exp OR 'hand disinfection':ab,ti OR 'hand cleansing':ab,ti OR 'hand hygiene':ab,ti OR 'hand sterility':ab,ti OR 'hand sanitization':ab,ti OR 'hand sanitizer':ab,ti OR 'hand gel':ab,ti 6. 'diarrhea'/exp OR 'diarrhoea':ab,ti OR 'diarrhea':ab,ti OR hepatitis:ab,ti 7. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	27 January 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included (but considered as indirect evidence). In case of preventive interventions: studies on primary prevention of injuries and diseases at household or community levels that describe interventions with a potential immediate effect. Studies on preventive programmes or campaigns that consist of training or provision of an information leaflet, booklet, sticker. Exclude: Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. Secondary or tertiary prevention. Interventions at policy level. Interventions based on drugs or vaccines. The following programmes: one-to-one programmes, home safety checks, free provision of materials, peer tutoring, information from medical doctors. Studies specifically intended for industrially specific situations (workplace related) **Outcome**: Include: health outcome measures (including adverse effects). Studies on the incidence of accidents. Exclude: studies on feasibility of or compliance with interventions (behavioural outcomes). Measures of knowledge or attitudes. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies. **Language**: Include: English **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Hübner, 2010, Germany	Experimental: randomized controlled trial	134 administrative officers who do not already apply hand disinfection at work were randomized in control (n=67, mean age 45.6 years) and intervention (n=67, mean age 43.6 years) group.	Intervention: alcohol-based hand rubs. Participants were advised to use it at least five times daily, especially after toilet use, blowing nose, before eating and after contact with ill colleagues, customers and archive material. Control: unchanged hand hygiene.	
Pickering, 2013, USA	Experimental: randomized controlled trial	1364 students (ages 5-13) in 6 schools in Nairobi, Kenya. Schools were randomly assigned to receive a hand washing with soap intervention (n=460), an alcohol-based hand sanitizer intervention (n=435) or no intervention (n=469)	Interventions: 1) Hand washing with soap or 2) alcohol-based hand sanitizer: an initial teacher training session followed by the installation of soap or sanitizer wall dispensers. Control: No intervention	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Absenteeism due to diarrhoea	Alcohol based hand rubs vs unchanged hand hygiene	<u>Statistically significant:</u> 1/64 vs 8/65 OR: 0.11, 95%CI[0.01;0.93] (p<0.05) *In favour of alcohol-based hand rubs*	1, 64 vs 65 §	Hübner 2010
Diarrhoea		Not statistically significant: 8/64 vs 15/65 OR: 0.48, 95%CI[0.19;1.22] (p≥0.05)		
	1. Hand washing with soap 2. Alcohol-based hand sanitizer 3. No intervention	Not statistically significant: 2 vs 3: RR: 0.75, 95%CI [0.52; 1.10] (p=0.14) ¥ Not statistically significant: 2 vs 1: RR: 0.89, 95%CI [0.61; 1.30] (p=0.56) ¥	1, 460 vs 435 vs 469	Pickering, 2013
Any loose/watery stool in 24 hours		Not statistically significant: 2 vs 3: RR: 0.87, 95%CI [0.72; 1.04] (p=0.12) ¥ <u>Statistically significant:</u> 2 vs 1: RR: 0.80, 95%CI [0.67; 0.95] (p=0.01) *In favour of alcohol-based hand sanitizer*		

*Calculations done by the reviewer(s) using Review Manager software

¥ Imprecision (large variability of results)

† Imprecision (lack of data)

§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Hübner, 2010	No, participants were randomized based on the frequency of customer contact and work with paper documents, since these are the most relevant covariants.	Yes, but irrelevant (participants could not be blinded for the intervention)	No	No	Conflicts of interest: 1 author is employed by the manufacturer of the hand gels, 2 authors received financial support for research from the manufacturer.
Pickering, 2013	Unclear, not specified in the article	Yes, but irrelevant (participants could not be blinded for the intervention)	No	No	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	
Imprecision	-1	Limited sample sizes/large variability of the results
Inconsistency	0	
Indirectness	0	
Publication bias	-1	Conflict of interest in one study
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is limited evidence from 2 experimental studies in favour of alcohol based hand sanitizers (Hübner 2010, Pickering 2013). It was shown that the use of alcohol-based hand rubs resulted in a statistically significant decrease of absenteeism due to diarrhoea, compared to normal hand hygiene practices (Hübner 2010). It was shown that alcohol-based hand sanitizers resulted in a statistically significant decrease of watery stools in 24 hours compared to hand washing with soap (Pickering 2013). A statistically significant decrease of diarrhoea, using alcohol-based hand sanitizer, compared to no hand gel, could not be demonstrated (Hübner 2010, Pickering 2013). Evidence is of low quality and results of these studies are imprecise due to limited sample size and/or large variability of results.
Reference(s)	**Articles** Hübner N, Hübner C, Wodny M, Kampf G, Kramer A. *Effectiveness of alcohol-based hand disinfectants in a public administration: Impact on health and work performance related to acute respiratory symptoms and diarrhoea.* BMC Infect Dis 2010, 10:250 Pickering AJ, Davis J, Blum AG, Scalmanini J, Oyier B, Okoth G, Breiman RF, Ram PK. *Access to waterless hand sanitizer improves student hand hygiene behavior in primary schools in Nairobi, Kenya.* Am J Trop Med Hyg 2013, 89(3): 411-418

Diarrhoea – Water purification (Prevention)

Question (PICO)	In humans (P), is water purification (I) compared to not doing this (C) effective to prevent diarrhoea (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search term: [mh "Diarrhea"] A Cochrane systematic review of 2015 was included.
Search date	18 January 2016
In/Exclusion criteria	**Population**: Include: adults and children **Intervention**: Include: interventions to purify water, relevant for travellers, including chlorination and filtration (ceramic filtration, sand filtration or Lifestraw®); Exclude: interventions relevant for developing countries; Plumbed filtration. **Outcome**: Include: diarrhoea **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: conference abstracts, case series, cross-sectional studies (studies collecting information concerning type of car and injury in health insurance companies), animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline)

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Clasen, 2015, USA	(Cochrane) Systematic review	55 studies (45 cluster-RCTs, 2 quasi-RCTs, and 8 CBA studies) including 84023 participants. 9 studies only included children under 5 years. 3 studies only included adults.	Interventions aimed at improving the microbiologic quality of drinking water, such as: physical removal of pathogens (filtration, adsorption, or sedimentation). Chemical treatment to kill or deactivate pathogens (most commonly with chlorine). Disinfection by heat (boiling or pasteurization) or UV radiation (solar disinfection, or artificial UV lamps). Combination of these approaches (filtration or flocculation combined with disinfection). Control: no intervention or dummy intervention [only data concerning interventions relevant for travellers were extracted, i.e. filtration, chlorination and flocculation (23 studies in total)].	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Diarrhoea episodes	Chlorination vs control	Statistically significant: RR: 0.72, 95%CI [0.61;0.84] (p=0.000053) *In favour of chlorination*	19, 19567 vs 15127	Clasen 2015
	Ceramic filtration vs control	Statistically significant: RR: 0.39, 95%CI [0.29;0.53] (p<0.00001) *In favour of ceramic filtration*	12, 3556 vs 2207	
	Sand filtration vs control	Statistically significant: RR: 0.47, 95%CI [0.39;0.57] (p<0.00001) *In favour of sand filtration*	5, 2743 vs 2761	
	Lifestraw® vs control	Statistically significant: RR: 0.69, 95%CI [0.51;0.93] (p=0.015) *In favour of Lifestraw®*	3, 1577 vs 1682	
	Flocculation and disinfection vs control	Statistically significant: RR: 0.69, 95%CI [0.58;0.82] (p=0.000037) *In favour of flocculation and disinfection*	6, 7667 vs 4121	

* Calculations done by the reviewer(s) using Review Manager software

¥ Imprecision (large variability of results)

† Imprecision (lack of data)

§ Imprecision (limited sample size or low number of events)

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See systematic review; lack of blinding
Imprecision	0	
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Moderate [B]**	

Conclusion	There is evidence in favour of chlorination, ceramic, sand or Lifestraw® filtration and flocculation and disinfection to purify water. It was shown that chlorination, ceramic, sand or Lifestraw® filtration and flocculation and disinfection of water resulted in a statistically significant decrease of diarrhoea compared to not doing this (Clasen 2015). Evidence is of moderate quality.
Reference(s)	**Systematic review** Clasen T, Roberts I, Rabie T, Schmidt W, Cairncross S. *Interventions to improve water quality for preventing diarrhoea*. Cochrane Database Syst Rev 2015, issue 10, 3:CD004794

Diarrhoea – Lactose avoidance (First Aid)

Question (PICO)	In humans with diarrhoea (P), is lactose avoidance (I) compared to not avoiding lactose effective and feasible to influence survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of the symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search term: [mh "Diarrhoea"] A Cochrane systematic review of 2013 was included.
Search date	23 May 2016
In/Exclusion criteria	**Population**: Include: people with acute diarrhoea of all ages. **Intervention**: Include: Lactose-free versus lactose-containing (at least 2%) milk, milk products, or foodstuffs or diluted (by at least 50%) versus undiluted lactose containing milk, milk products, or foodstuffs (given for > 24 hours) **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year:** Include: all years

Characteristics of included studies

Author, year Country	Study design	Population	Comparison	Remarks
MacGillivray, 2013, UK	Systematic review	33 trials including 2973 children less than 5 years old with acute diarrhoea. 22 trials compared outcomes for children given a lactose-free feed with those for children given a lactose-containing feed and 11 trials compared outcomes for children fed a diluted milk feed with those for children given an undiluted milk feed.	Lactose-free vs lactose-containing (at least 2%) milk, milk products or foodstuffs	Cochrane systematic review. Content assessed as up-to-date: 14 May 2013.

		Both studies performed in low and middle-income and high-income countries were included in the systematic review.		

Synthesis of findings

Outcome	Comparison/Risk factor	Effect Size	#studies, # participants	Reference
Duration of diarrhoea (hours)	Lactose-free vs lactose-containing milk products or foodstuffs	Statistically significant: 80.41±67.18 vs 97.63±75.83 ** MD: -17.77, 95%CI [-25.32;-10.21] (p<0.00001) *In favour of lactose-free products*	16, 740 vs 727	MacGillivray, 2013
Treatment failure		Statistically significant: 70/781 vs 113/689 RR: 0.52, 95%CI [0.39;0.68] (p<0.00001) *In favour of lactose-free products*	18, 781 vs 689	
Need for hospitalization		Not statistically significant: 1/20 vs 4/63 § RR: 0.79, 95%CI [0.09;6.65] ¥ (p=0.83) *	1, 20 vs 63	
Duration of hospital stay (days)		Not statistically significant: 6.76±3.63 vs 6.93 ±6.54 ** MD: -0.31, 95%CI [-0.83;0.21] ¥ (p=0.24)	5, 132 vs 114 §	
Stool volume (g/kg body weight/day)		Not statistically significant: 69.81±49.72 vs 72.58±54.78 ** MD: - 9.23, 95%CI [-32.61;14.14] ¥ (p=0.44)	3, 100 vs 94 §	
Duration of diarrhoea (hours)	Diluted (by at least 50%) versus undiluted lactose-containing milk, milk products, or foodstuffs	Not statistically significant: 69.84±62.18 vs 72.43±62.24 ** MD: -2.01, 95% CI [-9.71;5.68] (p=0.61) ¥	5, 238 vs 232	

Treatment failure		Statistically significant: 39/346 vs 59/341 RR: 0.65, 95%CI [0.45;0.94] (p=0.022) *In favour of diluted milk*	9, 346 vs 341	
Duration of hospital stay (days)		Not statistically significant: 4.50±2.39 vs 4.23±2.18 ** MD: -0.17, 95%CI [-0.50;0.16] (p=0.32) ¥	9, 405 vs 399	
Number of stools per day		Not statistically significant: 4.65±5.0 vs 5.19± 5.01 ** MD: 0.21, 95%CI [-0.21;0.57] (p=0.59) ¥	4, 208 vs 209	

Mean ± SD (unless otherwise indicated)
* Calculations done by the reviewer(s) using Review Manager software
¥ Imprecision (large variability of results)
† Imprecision (lack of data)
§ Imprecision (limited sample size or low number of events)
** Calculations done by reviewers in Excel template (weighed mean ± pooled SD)

Level of evidence

	High [A]	Downgrading due to
Limitations of study design	-1	See systematic review
Imprecision	-1	Limited sample size and large variability of results.
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Low [C]**	

Conclusion(s)	Lactose-free vs lactose-containing milk products or foodstuffs There is limited evidence in favour of lactose-free milk products: It was shown that lactose avoidance resulted in a statistically significant decrease of duration of diarrhoea and treatment failure, compared to not avoiding lactose (MacGillivray 2013). A statistically significant decrease of hospitalization, duration of hospital stay or stool volume, using lactose avoidance compared to not avoid lactose could not be demonstrated (MacGillivray 2013). Evidence is of low quality and results cannot be considered precise due to limited sample size, lack of data and/or large variability of results. Diluted (by at least 50%) versus undiluted lactose-containing milk, milk products, or foodstuffs

	There is limited evidence in favour of diluted lactose-containing milk: It was shown that diluted lactose-containing milk resulted in a statistically significant decrease of treatment failure, compared to undiluted lactose containing milk (MacGillivray 2013). A statistically significant decrease of duration of diarrhoea, duration of hospital stay or number of stools per day, using diluted lactose containing milk compared to undiluted lactose containing milk could not be demonstrated (MacGillivray 2013). Evidence is of low quality and results cannot be considered precise due to limited sample size, lack of data and/or large variability of results.
Reference(s)	**Systematic review** MacGillivray S, Fahey T, McGuireW. *Lactose avoidance for young children with acute diarrhea*. Cochrane Database of Systematic Reviews 2013, Issue 10. Art. No.: CD005433.

Diarrhoea - Amylase resistant starch oral rehydration solution (ORS) (First Aid)

Question (PICO)	In humans with diarrhoea (P), is using amylase resistant starch ORS (I) compared to standard ORS effective to influence survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of the symptoms (O)?
Search Strategy	Databases **Search for systematic reviews:** **The Cochrane Library**(systematic reviews and controlled trials) using the following search strategy: 1. [mh diarrhea] OR [mh dehydration] OR diarr*:ti,ab,kw OR dehydrat*:ti,ab,kw 2. [mh "fluid therapy"] OR rehydr*:ti,ab,kw OR ORS:ti,ab,kw OR hydrat*:ti,ab,kw 3. #1AND#2 **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Diarrhea"[Mesh] OR "Dehydration"[Mesh] OR diarr*[TIAB] OR dehydrat*[TIAB] 2. "Fluid Therapy"[Mesh] OR "rehydration solutions"[Mesh] OR ORS[TIAB] OR hydrat*[TIAB] OR rehydr*[TIAB] 3. ((((((((((Meta-Analysis as Topic[Mesh])) OR ((meta analy*[TIAB]))) OR ((metaanaly*[TIAB]))) OR ((Meta-Analysis[Publication Type]))) OR ((systematic review*[TIAB] OR systematic overview*[TIAB]))) OR ((Review Literature as Topic[Mesh])))) OR ((cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB]))) OR ((reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB]))) OR ((((selection criteria[TIAB] OR data extraction[TIAB])) AND ((Review[PT]))))) NOT ((Comment[PT] OR Letter[PT] OR Editorial[PT] OR animal[Mesh] NOT (animal[Mesh] AND human[Mesh]))) 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'Diarrhea'/exp OR 'Dehydration'/exp OR diarr*:ab,ti OR dehydrat*:ab,ti 2. 'oral rehydration therapy'/exp OR 'oral rehydration solution'/exp OR ORS:ab,ti OR hydrat*:ab,ti OR rehydr*:ab,ti 3. 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR

	'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti 4. 1-3 AND
Search date	08 February 2016
In/Exclusion criteria	**Population**: Include: people with acute diarrhoea of all ages. **Intervention**: Include: amylase resistant starch-ORS. Exclude: all other ORS solutions. **Comparison:** Include: reduced osmolarity ORS (≤270 mOsm/l). Exclude: hyperosmolar ORS (> 310 mOsm/l). **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year Country	Study design	Population	Comparison	Remarks
Gregorio, 2009, Philippines	Systematic review	44 RCT's including 4214 participants. 27 studies in children, 5 studies in adults and 2 studies in both children and adults. [Data from 1 RCT were extracted].	ORS in which glucose was replaced by a commercial or local preparation of a polymer versus standard ORS with glucose. [only studies comparing amylase resistant starch-based ORS versus sodium reduced (≤ 270 mOsm/l) ORS were included; only data of amylase resistant starch-based ORS were extracted].	Cochrane systematic review 2009. Review content assessed as up-to-date: 10 November 2008.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Unscheduled use of intravenous fluids	Amylase resistant starch-based ORS vs glucose based-ORS ≤270 mOsm/l	Not statistically significant: 9/25 vs 12/25 § RR: 0.75, 95%CI [0.39;1.46] (p=0.3865)* ¥	1, 25 vs 25 (Ramakrishna 2008)	Gregorio 2009
Hyponatraemia		Not statistically significant: 3/25 vs 2/25 § RR: 1.50, 95%CI [0.27;8.22] (p=0.6404)* ¥		

* Calculations done by the reviewer(s) using Review Manager software
¥ Imprecision (large variability of results)
§ Imprecision (low number of events)

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See systematic review
Imprecision	-1	Low number of events, large variability of results.
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final Moderate [B]**	

Conclusion(s)	There is limited evidence neither in favour of the intervention nor the control. A statistically significant decrease in unscheduled use of intravenous fluids or in hyponatraemia using amylase resistant starch-based ORS (Gregorio 2009) could not be demonstrated. Evidence is of moderate quality and results are imprecise due to low number of events and large variability of results.
Reference(s)	**Systematic review** Gregorio GV, Gonzales ML, Dans LF, Martinez EG. *Polymer-based oral rehydration solution for treating acute watery diarrhoea*. Cochrane Database Syst Rev 2009;(2):CD006519.

Diarrhoea - Amino acid based oral rehydration solution (ORS) (First Aid)

Question (PICO)	In victims with diarrhoea (P) is intake of amino acid based-ORS (I) compared to standard ORS effective to influence survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of the symptoms (O)?
Search Strategy	Databases **Cochrane Library:** 1. [mh diarrhea] OR [mh dehydration] OR diarr*:ti,ab,kw OR dehydrat*:ti,ab,kw 2. [mh "fluid therapy"] OR rehydr*:ti,ab,kw OR ORS:ti,ab,kw OR hydrat*:ti,ab,kw 3. [mh "amino acids"] OR [mh alanine] OR [mh glycine] OR Alanine*:ab,ti,kw OR glycine*:ab,ti,kw OR [mh "Zea mays"] OR maize*:ab,ti,kw OR [mh "Lens Plant"] OR lentil*:ab,ti,kw OR [mh Zinc] OR Zinc*:ab,ti,kw 4. #1AND#2AND#3

	Pubmed: 1. "Diarrhea"[Mesh] OR "Dehydration"[Mesh] OR diarr*[TIAB] OR dehydrat*[TIAB] 2. "Fluid Therapy"[Mesh] OR "rehydration solutions"[Mesh] OR ORS[TIAB] OR hydrat*[TIAB] OR rehydr*[TIAB] 3. "Amino acids"[Mesh] OR "Alanine"[Mesh] OR Alanine*[TIAB] OR "Glycine"[Mesh] OR Glycine*[TIAB] OR "Zea mays"[Mesh] OR maize*[TIAB] OR "lens plant"[Mesh] OR lentil*[TIAB] OR Zinc[Mesh] OR zinc*[TIAB] 4. 1-3 AND **Embase:** 1. 'Diarrhea'/exp OR 'Dehydration'/exp OR diarr*:ab,ti OR dehydrat*:ab,ti 2. 'oral rehydration therapy'/exp OR 'oral rehydration solution'/exp OR ORS:ab,ti OR hydrat*:ab,ti OR rehydr*:ab,ti 3. 'alanine'/exp OR Alanine*:ab,ti OR 'glycine'/exp OR glycine*:ab,ti OR 'maize'/exp OR maize*:ab,ti OR 'lentil'/exp OR lentil*:ab,ti OR 'zinc'/exp OR zinc*:ab,ti 4. 1-3 AND
Search date	29 April 2016
In/Exclusion criteria	**Population**: Include: people with acute diarrhoea of all ages. **Intervention**: Include: amino acid based-ORS. Exclude: ORS without amino acids **Comparison:** Include: reduced osmolarity ORS (≤ 270 mOsm/l). Exclude: hyperosmolar ORS (> 310 mOsm/l). **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year Country	Study design	Population	Comparison	Remarks
Alam, 2011, India	Experimental: randomized controlled trial	50 infants and young children: 25 in the study group and 25 in the control group. The study patients were selected from among male children, aged 6-36 months, who attended the Dhaka Hospital of ICDDR,B during July 2007–June 2008, with a history of acute watery diarrhoea of	L-isoleucine-added ORS (WHO and United Nations Children's Fund-recommended hypo-osmolar glucose-ORS, (Na-75 mmol/l, Cl-65mmol/l, K-20 mmol/l, citrate-10 mmol/l, and glucose-75 mmol/l) plus L-isoleucine-2 g/l, calculated osmolality: 252 mosmol/l) vs ORS without L-isoleucine (control) ORS	

		less than 48 hours' duration with some dehydration.		
Rabbani, 2005, India	Experimental: randomized controlled trial	126 male adults, 15–60 years old. The study was conducted at the Dhaka Hospital of the Centre for Health and Population Research at the International Centre for Diarrheal Disease Research, Bangladesh (ICDDR,B) during November 1999–June 2001. The patients were selected from the outpatient department and were admitted into the research ward for 72 h.	ORS solution (CeraLyte-90,255 mOsm/l, CERA Products) supplemented with l-histidine (2.5 g/l of ORS, Ajinomoto Chemical) vs CeraLyte-90 without l-histidine	As a standard antimicrobial treatment for cholera, oral ciprofloxacin was given to all patients at a dose of 500 mg every 12 h for 3 days, beginning at the time of admission into the study.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
L-isoleucine-added ORS				
Stool output (g) day 1	L-isoleucine-added ORS vs ORS without L-isoleucine (control) ORS	Not statistically significant: 560±240 vs 563±409 MD: -3.0, 95%CI [-189;183] (p=0.94)	1, 25 vs 25 §	Alam 2011
Stool output (g) day 2		Not statistically significant: 407±284 vs 515±316 MD:-108, 95%CI [-285;71] (p=0.23) ¥		
Stool output (g) day 3		Statistically significant: 388±261 vs 653±446 MD: -265, 95%CI [-509;-20] (p=0.035) *In favour of L-isoleucine-added ORS*		
Duration (hours) of diarrhoea		Not statistically significant:		

		74±38 vs 75±42 MD:-1.0, 95%CI [-17;25] (p=0.96)		
L-histidine-supplemented ORS				
Stool output (ml/kg) 32-48h	L-histidine-supplemented ORS vs unsupplemented-ORS	Statistically significant: 11.5±6.9 vs 18.8±16.0 MD: -7.30, 95%CI [14.80;22.80] (p=0.0012) * *In favour of L-histidine-based ORS*	1, 62 vs 64 §	Rabbani, 2005
Stool output (ml/kg) 40-48 h		Statistically significant: 6.7±4.4 vs 11.5±9.7 MD: -4.8, 95%CI [-7.42;-2.18] (p=0.0005) * *In favour of L-histidine-based ORS*		
Stool output (ml/kg) 56-64 h		Not statistically significant: 6.3±5.8 vs 7.8±4.1 MD: -1.5, 95%CI [-3.26;0.26] (p=0.10) *		
Unscheduled intravenous rehydration 0-24 h		Statistically significant: 82.5± 44.4 vs 158.6±72.2 MD: -76.10, 95%CI [-96.96; -55.24] (p<0.00001) * *In favour of L-histidine-based ORS*		
Unscheduled intravenous rehydration 24- 48 h		Not statistically significant: 41.6±40.4 vs 52.5±22.1 MD: -10.90, 95%CI [-22.32;0.52] (p=0.06) *		
Reduction duration of diarrhoea (h)	L-histidine-supplemented ORS vs unsupplemented-ORS	Statistically significant: 42.7±1.7 vs 47.0±1.8 MD: -4.30, 95%CI [-4.91;-3.68] (p<0.00001) * *In favour of L-histidine-based ORS*		

* Calculations done by the reviewer(s) using Review Manager software

¥ Imprecision (large variability of results)
§ Imprecision (limited sample size)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Alam, 2011	No, randomisation list	No, double blind	No	No	No
Rabbani, 2005	No, a computer-generated table of random numbers was used to assign the patients	No, double blind	No	No	No

Level of evidence

	High [A]	Downgrading due to
Limitations of study design	0	
Imprecision	-1	Large variability of results and limited sample sizes
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Moderate [B]**	

Conclusion(s)	L-isoleucine-added ORS There is evidence in favour of L-isoleucine-added ORS. It was shown that L-isoleucine ORS resulted in a statistically significant decrease of stool output on day 3, compared to unsupplemented ORS. A statistically significant decrease of stool output at day 1, stool output at day 2, and duration of diarrhoea, using L-isoleucine added ORS compared to unsupplemented ORS, could not be demonstrated (Alam 2011). Evidence is of moderate quality. L-histidine-supplemented ORS There is evidence in favour of L-histidine-supplemented ORS. It was shown that L-histidine ORS resulted in a statistically significant decrease of stool output, 32-48h, stool output, 40-48 h, unscheduled intravenous rehydration 24- 48 h, reduction duration of diarrhoea, compared to unsupplemented ORS (Rabbani 2005). It was shown that L-histidine-supplemented ORS did not result in a statistically significant difference of stool output (56-64 h) and unscheduled intravenous rehydration 0-24 h, compared to unsupplemented ORS (Rabbani 2005). Evidence is of moderate quality.
Reference(s)	**Articles** Alam NH, Raqib R, Ashraf H, Qadri F, Ahmed S, Zasloff M et al. *L-isoleucine-supplemented oral rehydration solution in the treatment of acute diarrhoea in children: a randomized controlled trial.* J Health Popul Nutr 2011, 29(3):183-190. Rabbani GH, Sack DA, Ahmed S, Peterson JW, Saha SK, Marni F et al. *Antidiarrheal effects of L-histidine-supplemented rice-based oral rehydration solution in the treatment of male adults with severe cholera in Bangladesh: a double-blind, randomized trial.* J Infect Dis 2005, 191(9):1507-1514.

Diarrhoea - Lentil-based oral rehydration solution (ORS) (First Aid)

Question (PICO)	In victims with diarrhoea (P) is intake of lentil-based ORS (I) compared to not using this effective to influence survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of the symptoms (O)?
Search Strategy	Databases **Cochrane Library:** 1. [mh diarrhea] OR [mh dehydration] OR diarr*:ti,ab,kw OR dehydrat*:ti,ab,kw 2. [mh "fluid therapy"] OR rehydr*:ti,ab,kw OR ORS:ti,ab,kw OR hydrat*:ti,ab,kw 3. [mh "amino acids"] OR [mh alanine] OR [mh glycine] OR Alanine*:ab,ti,kw OR glycine*:ab,ti,kw OR [mh "Zea mays"] OR maize*:ab,ti,kw OR [mh "Lens Plant"] OR lentil*:ab,ti,kw OR [mh Zinc] OR Zinc*:ab,ti,kw 4. #1AND#2AND#3 **Pubmed:** 1. "Diarrhea"[Mesh] OR "Dehydration"[Mesh] OR diarr*[TIAB] OR dehydrat*[TIAB] 2. "Fluid Therapy"[Mesh] OR "rehydration solutions"[Mesh] OR ORS[TIAB] OR hydrat*[TIAB] OR rehydr*[TIAB] 3. "Amino acids"[Mesh] OR "Alanine"[Mesh] OR Alanine*[TIAB] OR "Glycine"[Mesh] OR Glycine*[TIAB] OR "Zea mays"[Mesh] OR maize*[TIAB] OR "lens plant"[Mesh] OR lentil*[TIAB] OR Zinc[Mesh] OR zinc*[TIAB] 4. 1-3 AND **Embase:** 1. 'Diarrhea'/exp OR 'Dehydration'/exp OR diarr*:ab,ti OR dehydrat*:ab,ti 2. 'oral rehydration therapy'/exp OR 'oral rehydration solution'/exp OR ORS:ab,ti OR hydrat*:ab,ti OR rehydr*:ab,ti 3. 'alanine'/exp OR Alanine*:ab,ti OR 'glycine'/exp OR glycine*:ab,ti OR 'maize'/exp OR maize*:ab,ti OR 'lentil'/exp OR lentil*:ab,ti OR 'zinc'/exp OR zinc*:ab,ti 4. 1-3 AND
Search date	29 April 2016
In/Exclusion criteria	**Population**: Include: people with acute diarrhoea of all ages. **Intervention**: Include: lentil-based ORS. Exclude: ORS without lentils (mung beans). **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Jan, 1997, Pakistan	Experimental: Randomized controlled trial	76 children between 6 and 36 months of age, with acute watery diarrhoea of less than seven days were recruited.	Khitchri (59 g rice, 30 g Mong dal (lentils), 10 g oil, 1 g salt, 300 ml water) vs Dowdo; wheat-based gruel (125 g Atta (whole wheat flour), 1000 ml cows milk, 20 g oil, 8 g salt, 1000 ml water)	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Stool weight (g/kg body weight) at day 5	Khitchri (rice+lentil-based) vs Dowdo (wheat-based)	Not statistically significant: 56.5 vs 27.6 £†	1, 38 vs 38 §	Jan, 1997
Stool frequency (n/day) at day 5		Not statistically significant: 3 vs 2 £†		
Duration of hospitalization (hours)		Not statistically significant: 62 (20-216) vs 69.5 (19-192) £†		

£ No raw data/SD's available, effect size and CI cannot be calculated.

† Imprecision (lack of data)

§ Imprecision (limited sample size)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Jan, 1997	No, a pre-prepared list of computer generated random numbers was used.	No blinding	No	No	

Level of evidence

	High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample size and lack of data.
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Low [C]**	

Conclusion(s)	There is limited evidence neither in favour of the intervention nor the control: A statistically significant decrease of stool weight and stool frequency at day 5,and duration of diarrhoea using khitchri compared to dowdo, could not be demonstrated (Jan 1997). Evidence is of low quality and results of this this studies are imprecise due to limited sample size and lack of data.
Reference(s)	**Articles**

	Jan A, Rafi M, Mustafa S, Rasmussen ZA, Thobani S, Badruddin SH. *Evaluation of dowdo (wheat-milk gruel) in children with acute diarrhoea.* J Pak Med Assoc 1997, 47:12-16.

Diarrhoea – Malto-dextrin based oral rehydration solution (ORS) – (First Aid)

Question (PICO)	In humans with diarrhoea (P), is using malto-dextrin-based ORS (I) compared to standard ORS this effective to influence survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of the symptoms (O)?
Search Strategy	Databases **Search for systematic reviews:** **The Cochrane Library**(systematic reviews and controlled trials) using the following search strategy: 1. [mh diarrhea] OR [mh dehydration] OR diarr*:ti,ab,kw OR dehydrat*:ti,ab,kw 2. [mh "fluid therapy"] OR rehydr*:ti,ab,kw OR ORS:ti,ab,kw OR hydrat*:ti,ab,kw 3. #1AND#2 **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Diarrhea"[Mesh] OR "Dehydration"[Mesh] OR diarr*[TIAB] OR dehydrat*[TIAB] 2. "Fluid Therapy"[Mesh] OR "rehydration solutions"[Mesh] OR ORS[TIAB] OR hydrat*[TIAB] OR rehydr*[TIAB] 3. ((((((((((Meta-Analysis as Topic[Mesh])) OR ((meta analy*[TIAB]))) OR ((metaanaly*[TIAB]))) OR ((Meta-Analysis[Publication Type]))) OR ((systematic review*[TIAB] OR systematic overview*[TIAB]))) OR ((Review Literature as Topic[Mesh]))))) OR ((cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB]))) OR ((reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB]))) OR ((((selection criteria[TIAB] OR data extraction[TIAB])) AND ((Review[PT])))))) NOT ((Comment[PT] OR Letter[PT] OR Editorial[PT] OR animal[Mesh] NOT (animal[Mesh] AND human[Mesh]))) 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'Diarrhea'/exp OR 'Dehydration'/exp OR diarr*:ab,ti OR dehydrat*:ab,ti 2. 'oral rehydration therapy'/exp OR 'oral rehydration solution'/exp OR ORS:ab,ti OR hydrat*:ab,ti OR rehydr*:ab,ti 3. 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti 4. 1-3 AND
Search date	08 February 2016
In/Exclusion criteria	**Population**: Include: people with acute diarrhea of all ages. **Intervention**: Include: malto-dextin-based ORS. Exclude: all other based ORS solutions. **Comparison:** Include: reduced osmolarity ORS (≤ 270 mOsm/l). Exclude: hyperosmolar ORS (> 310 mOsm/l). **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects).

	Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year Country	Study design	Population	Comparison	Remarks
Gregorio, 2009, Philippines	Systematic review	44 RCT's including 4214 participants. 27 studies in children, 5 studies in adults and 2 studies in both children and adults. [Data from 3 RCT's were extracted].	ORS in which glucose was replaced by a commercial or local preparation of a polymer vs standard ORS with glucose. [only studies comparing maltodextrin-based ORS versus sodium reduced (≤ 270 mOsm/l) ORS were included; only data of maltodextrin ORS were extracted].	Cochrane systematic review 2009. Review content assessed as up-to-date: 10 November 2008.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Total stool output during first 24 h	Maltodextrin-based ORS vs glucose-based ≤ 270 mOsm/l ORS	Not statistically significant: 162.8±138.2 vs 135.4±107.9 MD: 27.40, 95%CI [-17.58;72.38] (p=0.2340)* ¥	1, 58 vs 59 § (Santos Ocampo 1993)	Gregorio, 2009
Duration of diarrhoea (h)		Not statistically significant: 52.6±32.2 57.2±37.3 MD: -4.60, 95%CI [-17.28;8.08] (p=0.4770)*		
Unscheduled use of intravenous fluids		Not statistically significant: 7/78 vs 9/80 §,	2, 78 vs 80 (Akbar 1991, El-Mougi 1996)	

		RR 0.79, 95%CI [0.31;2.02] ¥ (p=0.62)		

* Calculations done by the reviewer(s) using Review Manager software
¥ Imprecision (large variability of results)
§ Imprecision (limited sample size or low number of events)

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	
Imprecision	-1	Limited sample size, low number of events, and/or large variability of results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Moderate [B]**	

Conclusion(s)	There is evidence showing no difference between intervention and control: It was shown that maltodextrin based ORS did not result in a statistically significant difference of duration of diarrhoea, compared to reduced osmolarity (≤ 270 mOsm/l) glucose ORS. A statistically significant decrease in total stool output during first 24 h or unscheduled use of intravenous fluids using maltodextrin based ORS compared to reduced osmolarity ORS (≤ 270 mOsm/l) could not be demonstrated (Gregorio 2009). Evidence is of moderate quality and results of these studies are imprecise due to limited sample size, low number of events and/or large variability of results. Evidence is of moderate quality.
Reference(s)	**Systematic review** Gregorio GV, Gonzales ML, Dans LF, Martinez EG. *Polymer-based oral rehydration solution for treating acute watery diarrhoea*. Cochrane Database Syst Rev 2009;(2):CD006519.

Diarrhoea – Maize/millet based oral rehydration solution (ORS) (First Aid)

Question (PICO)	In victims with diarrhoea (P) is intake of maize-based ORS (I) compared to not using this effective to influence survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of the symptoms (O)?
Search Strategy	Databases **Cochrane Library:** 1. [mh diarrhea] OR [mh dehydration] OR diarr*:ti,ab,kw OR dehydrat*:ti,ab,kw 2. [mh "fluid therapy"] OR rehydr*:ti,ab,kw OR ORS:ti,ab,kw OR hydrat*:ti,ab,kw 3. [mh "amino acids"] OR [mh alanine] OR [mh glycine] OR Alanine*:ab,ti,kw OR glycine*:ab,ti,kw OR [mh "Zea mays"] OR maize*:ab,ti,kw OR [mh "Lens Plant"] OR lentil*:ab,ti,kw OR [mh Zinc] OR Zinc*:ab,ti,kw 4. #1AND#2AND#3 **Pubmed:** 1. "Diarrhea"[Mesh] OR "Dehydration"[Mesh] OR diarr*[TIAB] OR dehydrat*[TIAB] 2. "Fluid Therapy"[Mesh] OR "rehydration solutions"[Mesh] OR ORS[TIAB] OR hydrat*[TIAB] OR rehydr*[TIAB] 3. "Amino acids"[Mesh] OR "Alanine"[Mesh] OR Alanine*[TIAB] OR "Glycine"[Mesh] OR Glycine*[TIAB] OR "Zea mays"[Mesh] OR maize*[TIAB] OR "lens plant"[Mesh] OR lentil*[TIAB] OR Zinc[Mesh] OR zinc*[TIAB] 4. 1-3 AND

	Embase: 1. 'Diarrhea'/exp OR 'Dehydration'/exp OR diarr*:ab,ti OR dehydrat*:ab,ti 2. 'oral rehydration therapy'/exp OR 'oral rehydration solution'/exp OR ORS:ab,ti OR hydrat*:ab,ti OR rehydr*:ab,ti 3. 'alanine'/exp OR Alanine*:ab,ti OR 'glycine'/exp OR glycine*:ab,ti OR 'maize'/exp OR maize*:ab,ti OR 'lentil'/exp OR lentil*:ab,ti OR 'zinc'/exp OR zinc*:ab,ti 4. 1-3 AND
Search date	29 April 2016
In/Exclusion criteria	**Population**: Include: people with acute diarrhoea of all ages. **Intervention**: Include: maize based ORS and millet based ORS. Exclude: all other ORS. **Comparison:** Include: reduced osmolarity ORS (≤ 270 mOsm/l). Exclude: hyperosmolar ORS (> 310 mOsm/l). **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion(s)	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	Not applicable

Diarrhoea – Rice-based oral rehydration solution (ORS) (First Aid)

Question (PICO)	In humans with diarrhoea (P), is using rice-based ORS (I) compared to standard ORS effective to influence survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of the symptoms (O)?
Search Strategy	Databases **Search for systematic reviews:**

	The Cochrane Library(systematic reviews and controlled trials) using the following search strategy: 1. [mh diarrhea] OR [mh dehydration] OR diarr*:ti,ab,kw OR dehydrat*:ti,ab,kw 2. [mh "fluid therapy"] OR rehydr*:ti,ab,kw OR ORS:ti,ab,kw OR hydrat*:ti,ab,kw 3. #1AND#2 **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Diarrhea"[Mesh] OR "Dehydration"[Mesh] OR diarr*[TIAB] OR dehydrat*[TIAB] 2. "Fluid Therapy"[Mesh] OR "rehydration solutions"[Mesh] OR ORS[TIAB] OR hydrat*[TIAB] OR rehydr*[TIAB] 3. ((((((((((Meta-Analysis as Topic[Mesh])) OR ((meta analy*[TIAB]))) OR ((metaanaly*[TIAB]))) OR ((Meta-Analysis[Publication Type]))) OR ((systematic review*[TIAB] OR systematic overview*[TIAB]))) OR ((Review Literature as Topic[Mesh])))) OR ((cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB]))) OR ((reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB]))) OR ((((selection criteria[TIAB] OR data extraction[TIAB])) AND ((Review[PT]))))) NOT ((Comment[PT] OR Letter[PT] OR Editorial[PT] OR animal[Mesh] NOT (animal[Mesh] AND human[Mesh]))) 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'Diarrhea'/exp OR 'Dehydration'/exp OR diarr*:ab,ti OR dehydrat*:ab,ti 2. 'oral rehydration therapy'/exp OR 'oral rehydration solution'/exp OR ORS:ab,ti OR hydrat*:ab,ti OR rehydr*:ab,ti 3. 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti 4. 1-3 AND
Search date	08 February 2016
In/Exclusion criteria	**Population**: Include: people with acute diarrhea of all ages. **Intervention**: Include: rice-based ORS ≤270mmol/L Exclude: all other ORS solutions **Comparison:** Include: reduced osmolarity ORS (≤ 270 mOsm/l). Exclude: hyperosmolar ORS (> 310 mOsm/l). **Outcome:** Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values.

	Language: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year Country	Study design	Population	Comparison	Remarks
Gregorio, 2009, Philippines	Systematic review	44 RCT's including 4214 participants. 27 studies in children, 5 studies in adults, 2 studies in both children and adults. [Data from 5 RCT's were extracted]	ORS in which glucose was replaced by a commercial or local preparation of a polymer [only studies comparing rice-based ORS versus sodium reduced (≤ 270 mOsm/l) ORS were included; only data of rice-based ORS were extracted]	Cochrane systematic review 2009. Uncooked, cooked, powdered or pop rice was used. Review content assessed as up-to-date: 10 November 2008.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Total stool output: during first 24 hours	Rice-based vs glucose-based ORS ≤ 270 mOsm/l	Statistically significant: 77.4±47 vs 102±33 MD: -24.60, 95%CI [-40.69;-8.51] (p=0.032)* *In favour of rice-based ORS*	1, 48 vs 51 § (Nanulescu 1999)	Gregorio 2009
Duration of diarrhoea (hours)		Statistically significant: 1. 36.5±12.8 vs 46.9±11.9 MD: -10.40, 95%CI [-16.84;-3.96] (p=0.0024)* 2. 29.34±4.83 vs 33.9±3.77 MD: -4.56 95%CI [-7.32;-1.80] (p=0.0025)* *In favour of rice-based ORS*. Not statistically significant: 3. 51±24 vs 54±40 3. MD: -3.00, 95%CI [-15.91;9.91] (p=0.6544)*	3, 1. 27 vs 30 § (Bhattacharya 1998) 2. 19 vs 19 § (Dutta 2000) 3. 48 vs 51 § (Nanulescu 1999)	
Unscheduled use of intravenous fluids		Statistically significant: 1. 1/93 vs 8/84 § RR: 0.11, 95%CI [0.01;0.88] (p=0.0378)* *In favour of rice-based ORS* Not statistically significant: 2. 5/48 vs 4/51 §	2, 1. 93 vs 48 (Maulen-radovan 2004) 2. 48 vs 51 (Nanulescu 1999)	

		RR: 1.33, 95%CI [0.38;4.66] (p=0.6571)* ¥		
Vomiting	Rice-based ORS vs glucose-based ORS ≤270 mOsm/l	Not statistically significant: 3. 6/31 vs 11/32 § RR: 0.56, 95%CI [0.24;1.34] (p=0.1718)* ¥	1, 31 vs 32 (Iyngkaran 1998)	

* Calculations done by the reviewer(s) using Review Manager software

¥ Imprecision (large variability of results)

§ Imprecision (limited sample size or low number of events)

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See systematic review, lack of blinding or blinding unclear
Imprecision	-1	Limited sample size, low number of events and/or large variability of results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion(s)	There is limited evidence in favour of rice-based-ORS. (In making this evidence conclusion, we place a higher value on the outcome of "total stool output", and on the two significant studies for the outcome "duration of diarrhea", compared to one study showing no difference). It was shown that rice-based ORS resulted in a statistically significant decrease of total stool output and duration of diarrhoea, compared to glucose-based ORS (≤ 270 mOsm/l) (Gregorio 2009). A statistically significant decrease in vomiting using rice based ORS compared to glucose-based ORS (≤ 270 mOsm/l) could not be demonstrated (Gregorio 2009). Evidence is of low quality and results of this study are imprecise due to limited sample size, low number of events and/or large variability of results.
Reference(s)	**Systematic review** Gregorio GV, Gonzales ML, Dans LF, Martinez EG. *Polymer-based oral rehydration solution for treating acute watery diarrhoea*. Cochrane Database Syst Rev 2009;(2):CD006519.

Diarrhoea – Sorghum-based oral rehydration solution (ORS) (First Aid)

Question (PICO)	In humans with diarrhoea (P), is using sorghum-based ORS (I) compared to standard ORS effective to influence survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of the symptoms (O)?
Search Strategy	Databases **Search for systematic reviews:** **The Cochrane Library**(systematic reviews and controlled trials) using the following search strategy: 1. [mh diarrhea] OR [mh dehydration] OR diarr*:ti,ab,kw OR dehydrat*:ti,ab,kw 2. [mh "fluid therapy"] OR rehydr*:ti,ab,kw OR ORS:ti,ab,kw OR hydrat*:ti,ab,kw 3. #1AND#2 **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Diarrhea"[Mesh] OR "Dehydration"[Mesh] OR diarr*[TIAB] OR dehydrat*[TIAB] 2. "Fluid Therapy"[Mesh] OR "rehydration solutions"[Mesh] OR ORS[TIAB] OR hydrat*[TIAB] OR rehydr*[TIAB]

	3. ((((((((((Meta-Analysis as Topic[Mesh])) OR ((meta analy*[TIAB]))) OR ((metaanaly*[TIAB]))) OR ((Meta-Analysis[Publication Type]))) OR ((systematic review*[TIAB] OR systematic overview*[TIAB]))) OR ((Review Literature as Topic[Mesh])))) OR ((cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB]))) OR ((reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB]))) OR ((((selection criteria[TIAB] OR data extraction[TIAB])) AND ((Review[PT])))))) NOT ((Comment[PT] OR Letter[PT] OR Editorial[PT] OR animal[Mesh] NOT (animal[Mesh] AND human[Mesh]))) 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'Diarrhea'/exp OR 'Dehydration'/exp OR diarr*:ab,ti OR dehydrat*:ab,ti 2. 'oral rehydration therapy'/exp OR 'oral rehydration solution'/exp OR ORS:ab,ti OR hydrat*:ab,ti OR rehydr*:ab,ti 3. 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti 4. 1-3 AND
Search date	08 February 2016
In/Exclusion criteria	**Population**: Include: people with acute diarrhoea of all ages. **Intervention**: Include: sorghum-based ORS. Exclude: all other ORS. **Comparison:** Include: reduced osmolarity ORS (≤ 270 mOsm/l). Exclude: hyperosmolar ORS (> 310 mOsm/l). **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) Publication year: Include: all years

Characteristics of included studies

Author, year Country	Study design	Population	Comparison	Remarks
Gregorio, 2009, Philippines	Systematic review	44 RCT's including 4214 participants. 27 studies in children, 5 studies in adults, 2 studies in both children and adults.	ORS in which glucose was replaced by a commercial or local preparation of a polymer vs standard ORS with glucose	Cochrane systematic review 2009. Review content assessed as up-to-

		[data from 2 RCT's were extracted].	[only studies comparing sorghum-based ORS versus sodium reduced (≤ 270 mOsm/l) ORS were included; only data of sorghum ORS were extracted].	date: 10 November 2008.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Total stool output during first 24 hours	Sorghum-based ORS vs glucose-based ORS ≤ 270 mOsm/l	Statistically significant: 162.8±138.2 vs 135.4±107.9 MD: -128, 95%CI [-207.66;-48.34] (p<0.00001)* *In favour of sorghum-based ORS*	1, 35 vs 42 § (Molla 1989)	Gregorio, 2009
Duration of diarrhoea (hours)		Not statistically significant: 46.7±35.97 vs 63.1±35.2 MD: -16.40, 95%CI [-33.57;0.77] (p=0.0660)*¥	1, 34 vs 32 § (Mustafa 1995)	

* Calculations done by the reviewer(s) using Review Manager software
¥ Imprecision (large variability of results)
§ Imprecision (limited sample size or low number of events)

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See systematic review, lack of blinding or blinding unclear.
Imprecision	-1	Limited sample size, low number of events, large variability in results.
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion(s)	There is limited evidence in favour of sorghum-based ORS. It was shown that sorghum-based ORS resulted in a statistically significant decrease in total stool output during first 24 h compared to glucose-based ORS (Gregorio 2009). A statistically significant decrease of duration of diarrhoea, using sorghum-based ORS compared to glucose-based ORS (≤ 270 mOsm/l), could not be demonstrated (Gregorio 2009). Evidence is of low quality and results cannot be considered precise due to limited sample size, low number of events and/or large variability of results.
Reference(s)	**Systematic review**

	Gregorio GV, Gonzales ML, Dans LF, Martinez EG. *Polymer-based oral rehydration solution for treating acute watery diarrhoea*. Cochrane Database Syst Rev 2009;(2):CD006519.

Diarrhoea – Wheat-based oral rehydration solution (ORS) (First Aid)

Question (PICO)	In humans with diarrhoea (P), is using wheat-based ORS (I) compared to standard ORS effective to influence survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of the symptoms (O)?
Search Strategy	Databases **Search for systematic reviews:** **The Cochrane Library**(systematic reviews and controlled trials) using the following search strategy: 4. [mh diarrhea] OR [mh dehydration] OR diarr*:ti,ab,kw OR dehydrat*:ti,ab,kw 1. [mh "fluid therapy"] OR rehydr*:ti,ab,kw OR ORS:ti,ab,kw OR hydrat*:ti,ab,kw 2. #1AND#2 **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Diarrhea"[Mesh] OR "Dehydration"[Mesh] OR diarr*[TIAB] OR dehydrat*[TIAB] 2. "Fluid Therapy"[Mesh] OR "rehydration solutions"[Mesh] OR ORS[TIAB] OR hydrat*[TIAB] OR rehydr*[TIAB] 3. ((((((((((Meta-Analysis as Topic[Mesh])) OR ((meta analy*[TIAB]))) OR ((metaanaly*[TIAB]))) OR ((Meta-Analysis[Publication Type]))) OR ((systematic review*[TIAB] OR systematic overview*[TIAB]))) OR ((Review Literature as Topic[Mesh])))) OR ((cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB]))) OR ((reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB]))) OR ((((selection criteria[TIAB] OR data extraction[TIAB])) AND ((Review[PT]))))) NOT ((Comment[PT] OR Letter[PT] OR Editorial[PT] OR animal[Mesh] NOT (animal[Mesh] AND human[Mesh]))) 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'Diarrhea'/exp OR 'Dehydration'/exp OR diarr*:ab,ti OR dehydrat*:ab,ti 2. 'oral rehydration therapy'/exp OR 'oral rehydration solution'/exp OR ORS:ab,ti OR hydrat*:ab,ti OR rehydr*:ab,ti 3. 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti 4. 1-3 AND
Search date	08 February 2016
In/Exclusion criteria	**Population**: Include: people with acute diarrhoea of all ages. **Intervention**: Include: wheat ORS; exclude all other ORS **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Comparison:** Include: reduced osmolarity ORS (≤270 mOsm/l). Exclude: hyperosmolar ORS (> 310 mOsm/l).

	Design: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year Country	Study design	Population	Comparison	Remarks
Gregorio, 2009, Philippines	Systematic review	44 RCT's including 4214 participants. 27 studies children, 5 studies in adults and 2 studies in both children and adults. [data from 2 RCT's were extracted].	ORS in which glucose was replaced by a commercial or local preparation of a polymer vs standard ORS with glucose [only studies comparing wheat-based ORS versus sodium reduced (≤ 270 mOsm/l) ORS were included; only data of wheat-based ORS were extracted].	Cochrane systematic review 2009. Review content assessed as up-to-date: 10 November 2008.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Total stool output during first 24 hours	Wheat-based ORS vs glucose-based ORS (≤ 270 mOsm/l)	Statistically significant: 1. 170±4.08 vs 290±12.2 MD: -120, 95%CI [-125.12;-114.85] (p<0.00001)* 2. 240±96 vs 343±51 MD: -103; 95%CI [-157.71,-48.29] (p=0.0005)* *In favour of Wheat-based ORS*	2, 1. 24 vs 24 § (Alam 1987) 2. 39 vs 42 § (Molla 1989)	Gregorio, 2009
Duration of diarrhea (hours)		Statistically significant: 80±1.22 vs 90±1.78 MD: -10, 95%CI [-10.86;-9.41] (p<0.00001)*	1, 24 vs 24 § (Alam 1987)	

		In favour of Wheat-based ORS		
Unscheduled use of intravenous fluid		Not statistically significant: 2/24 vs 2/24 § RR: 1, 95%CI [0.15;6.53] (p=1.00)* ¥	1, 24 vs 24 (Alam 1987)	

* Calculations done by the reviewer(s) using Review Manager software

¥ Imprecision (large variability of results)

§ Imprecision (limited sample size or low number of events)

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See systematic review, lack of blinding or blinding unclear.
Imprecision	-1	Limited sample size, low number of events and large variability of results.
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading low [C]**	

Conclusion(s)	There is limited evidence in favour of wheat-based ORS. It was shown that wheat-based ORS resulted in a statistically significant decrease in total stool output during first 24 h and duration of diarrhoea compared to glucose-based-ORS (Gregorio 2009). A statistically significant decrease of unscheduled use of intravenous fluid, using wheat-based ORS compared to glucose-based ORS (≤270 mOsm/l), could not be demonstrated (Gregorio 2009). Evidence is of low quality and results of these studies are imprecise due to limited sample size, low number of events and large variability of results.
Reference(s)	**Systematic review** Gregorio GV, Gonzales ML, Dans LF, Martinez EG. *Polymer-based oral rehydration solution for treating acute watery diarrhoea*. Cochrane Database Syst Rev 2009;(2):CD006519.

Diarrhoea – Zinc tablets (First Aid)

Question (PICO)	In humans with diarrhoea (P), is taking zinc tablets (I) compared to not taking zinc tablets effective for reducing the duration and recovery from diarrhoea (O)?
Search Strategy	Databases **Search for systematic reviews:** **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh diarrhea] OR [mh dehydration] OR diarr*:ti,ab,kw OR dehydrat*:ti,ab,kw 2. [mh "fluid therapy"] OR rehydr*:ti,ab,kw OR ORS:ti,ab,kw OR hydrat*:ti,ab,kw 3. #1AND#2 **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Diarrhea"[Mesh] OR "Dehydration"[Mesh] OR diarr*[TIAB] OR dehydrat*[TIAB] 2. "Fluid Therapy"[Mesh] OR "rehydration solutions"[Mesh] OR ORS[TIAB] OR hydrat*[TIAB] OR rehydr*[TIAB] 3. ((((((((((Meta-Analysis as Topic[Mesh])) OR ((meta analy*[TIAB]))) OR ((metaanaly*[TIAB]))) OR ((Meta-Analysis[Publication Type]))) OR ((systematic review*[TIAB] OR systematic overview*[TIAB]))) OR ((Review Literature as

	Topic[Mesh]))))) OR ((cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB])))) OR ((reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB]))) OR ((((selection criteria[TIAB] OR data extraction[TIAB])) AND ((Review[PT]))))))) NOT ((Comment[PT] OR Letter[PT] OR Editorial[PT] OR animal[Mesh] NOT (animal[Mesh] AND human[Mesh]))) 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'Diarrhea'/exp OR 'Dehydration'/exp OR diarr*:ab,ti OR dehydrat*:ab,ti 2. 'oral rehydration therapy'/exp OR 'oral rehydration solution'/exp OR ORS:ab,ti OR hydrat*:ab,ti OR rehydr*:ab,ti 3. 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti 4. 1-3 AND
Search date	08 February 2016
In/Exclusion criteria	**Population**: Include: people with acute diarrhoea of all ages. **Intervention**: Include: Oral zinc supplementation of any zinc salt at doses of 5 mg/day or more. Exclude: ORS plus zinc and food fortification interventions (such as milk fortification). **Comparison:** Include: Oral zinc supplementation of any zinc salt at doses of 5 mg/day or more for any duration vs no zinc supplementation (placebo). **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year Country	Study design	Population	Comparison	Remarks
Lazzerini, 2013, Italy	Systematic review	24 RCTs, enrolling 9128 children with acute diarrhoea.	Oral zinc supplementation of any zinc salt at doses of 5 mg/day or more for any duration	Cochrane review 2013. Review content assessed as up-to-date: 20 February 2012.

			vs no zinc supplementation (placebo). [only data for acute diarrhoea were extracted].	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Diarrhoea duration (h)	Zinc vs placebo	Statistically significant: 91.44±80.53 vs 92.97±76.08 ** MD: -12.63, 95%CI [-21.05;-4.21] (p=0.0033) *In favour of zinc*	19, 2269 vs 2177	Lazzerini, 2013
Diarrhoea on day 3 after intervention		Statistically significant: 226/782 vs 294/786 RR: 0.77, 95%CI, [0.67;0.89] (p=0.00027) *In favour of zinc*	4, 782 vs 786	
Diarrhoea on day 5 after intervention		Statistically significant: 72/869 vs 107/861 RR: 0.67, 95%CI [0.51;0.89] (p=0.0059) *In favour of zinc*	5, 869 vs 861	
Diarrhoea on day 7 after intervention		Statistically significant: 329/2750 vs 406/2778 RR: 0.82, 95%CI [0.72;0.94] (p=0.0033) *In favour of zinc*	13, 2750 vs 2778	
Stool frequency (stools/day)		Not statistically significant: 5.26±3.02 vs 5.55±3.17 ** MD: -0.05, 95%CI [-0.20;0.10] (p=0.54)	9, 1205 vs 1118	
Vomiting		Statistically significant: 557/2613 vs 344/2576 RR: 1.59, 95%CI [1.27;1.99] (p=0.03) *In favour of placebo*	12, 2613 vs 2576	

** Calculations done by reviewers in Excel template (weighed mean ± pooled SD)

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	
Imprecision	0	
Inconsistency	0	
Indirectness	-1	The majority of the data is from Asia, from countries at high risk of zinc deficiency, and may not be applicable elsewhere.
Publication bias	0	
QUALITY (GRADE)	**Final grading Moderate [B]**	

Conclusion(s)	There is evidence in favour of taking zinc tablets. It was shown that zinc resulted in a statistically significant decrease of diarrhoea duration, diarrhoea on day 3, day 5 or day 7 after zinc intake and vomiting compared to placebo (Lazzerni 2013). It was shown that zinc tablets did not result in a statistically significant difference of stool frequency, compared to placebo (Lazzerni 2013). Evidence is of moderate quality.
Reference(s)	**Systematic review** Lazzerini M, Ronfani L. *Oral zinc for treating diarrhoea in children*. Cochrane Database of Systematic Reviews 2013, Issue 1. Art. No.: CD005436.

Diarrhoea – Zinc-based oral rehydration solution (ORS) (First Aid)

Question (PICO)	In victims with diarrhoea (P) is intake of zinc-ORS (I) compared to using standard ORS effective to influence survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of the symptoms (O)?
Search Strategy	Databases **Cochrane Library:** (systematic reviews and controlled trials) using the following search strategy: 1. [mh diarrhea] OR [mh dehydration] OR diarr*:ti,ab,kw OR dehydrat*:ti,ab,kw 2. [mh "fluid therapy"] OR rehydr*:ti,ab,kw OR ORS:ti,ab,kw OR hydrat*:ti,ab,kw 3. [mh "amino acids"] OR [mh alanine] OR [mh glycine] OR Alanine*:ab,ti,kw OR glycine*:ab,ti,kw OR [mh "Zea mays"] OR maize*:ab,ti,kw OR [mh "Lens Plant"] OR lentil*:ab,ti,kw OR [mh Zinc] OR Zinc*:ab,ti,kw 4. #1AND#2AND#3 **Pubmed:** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Diarrhea"[Mesh] OR "Dehydration"[Mesh] OR diarr*[TIAB] OR dehydrat*[TIAB] 2. "Fluid Therapy"[Mesh] OR "rehydration solutions"[Mesh] OR ORS[TIAB] OR hydrat*[TIAB] OR rehydr*[TIAB] 3. "Amino acids"[Mesh] OR "Alanine"[Mesh] OR Alanine*[TIAB] OR "Glycine"[Mesh] OR Glycine*[TIAB] OR "Zea mays"[Mesh] OR maize*[TIAB] OR "lens plant"[Mesh] OR lentil*[TIAB] OR Zinc[Mesh] OR zinc*[TIAB] 4. 1-3 AND **Embase:** (via Embase.com interface) using the following search strategy: 1. 'Diarrhea'/exp OR 'Dehydration'/exp OR diarr*:ab,ti OR dehydrat*:ab,ti 2. 'oral rehydration therapy'/exp OR 'oral rehydration solution'/exp OR ORS:ab,ti OR hydrat*:ab,ti OR rehydr*:ab,ti

	3. 'alanine'/exp OR Alanine*:ab,ti OR 'glycine'/exp OR glycine*:ab,ti OR 'maize'/exp OR maize*:ab,ti OR 'lentil'/exp OR lentil*:ab,ti OR 'zinc'/exp OR zinc*:ab,ti 4. 1-3 AND
Search date	29 April 2016
In/Exclusion criteria	**Population**: Include: people with acute diarrhoea of all ages. **Intervention**: Include: zinc-fortified-ORS. Exclude: zinc tablets or other ORS solutions without zinc. **Comparison:** Include: reduced osmolarity ORS (≤ 270 mOsm/l), or if no information on the osmolarity is given, papers published after the year 2002. Exclude: hyperosmolar ORS (> 310 mOsm/l), or if no information on the osmolarity is given, papers published before the year 2002. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: if no information on the osmolarity is given, include publications after year 2002.

Characteristics of included studies

Author, year Country	Study design	Population	Comparison	Remarks
Gregorio, 2007, Philippines	Experimental: randomized controlled trial	117 children between 2 and 59 months old with diarrhoea <7 days duration and no evidence of dehydration. Patients were recruited at the Emergency Room (ER) of the institution and from two satellite centres (San Andres and Paco local health units) within 5 km from study site.	20 mg zinc sulfate tablet per day for 14 days along with standard WHO-ORS vs WHO-ORS only. The zinc tablets, taken 2 hours after food intake, were dissolved in water or milk before administration or were taken without dissolving them by older children.	No evidence of dehydration
Karamyyar, 2013, Iran	Experimental: randomized controlled trial	379 9-month to 5-year-old children who were admitted with acute watery diarrhoea and moderate dehydration to the Children Ward of Motahari Hospital,	zinc syrup ((1 ml/kg/day), which contained 1 mg zinc sulphate/1ml), plus ORS vs	

		Urmia, Iran in 2008 were recruited.	ORS plus placebo (1 ml/kg/day)	
Tran, 2015, Australia	Experimental: randomized controlled trial	76 children (34 females, 42 males; age, 2.7±2.7 years) were enrolled presenting to the Women's and Children's Health Network Emergency Department with diarrhoea between May 2004 and June 2006. Subjects aged 6 months to 12 years were eligible to participate in the study if they were clinically diagnosed with diarrhoea (defined as the passage of 3 or more loose/ watery stools in a 24-hour period) with or without vomiting.	All were treated for 5 days following admission with either: zinc (Zn sulphate to a total of 3 mg elemental zinc) fortified rice-based ORS (6 g rice powder) vs no zinc-fortified rice-ORS (no added Zn).	
Wadhwa, 2011, India	Experimental: randomized controlled trial	500 northern Indian children ages 1 to 35 months with diarrhoea <7 days' duration attended the diarrhoea treatment units of the All India Institute of Medical Sciences and Deen Dayal Upadhyay Hospital in New Delhi between December 2003 and March 2007.	Zinc ORS (245 mOsm/l) vs standard ORS (245 mOsm/l)	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Zinc-fortified rice-ORS				
Median diarrhoea duration (days)	Zinc fortified-rice based ORS vs rice based ORS	Not statistically significant: 1.2±1.5 vs 1.3±1.5, MD:-0.1, 95%CI [-0.87;0.67] (p=0.08) *¥	1, 29 vs 29 §	Tran, 2015
Mean n of loose stools, day 1		Not statistically significant: 3.7±2.8 vs 4.4±2.6, MD:-0.7, 95%CI [-2.09;0.69] (p=0.33) *		
Mean n of loose stools, day 2		Not statistically significant: 2.3±2.4 vs 2.1±2.4, MD: 0.20, 95%CI [-1.04;1.44],		

		(p=0.75) *¥		
Mean n of loose stools, day 3		Not statistically significant: 1.7±2.3 vs 0.8±1.6, MD: 0.9, 95%CI [-1.12;1.92], (p=0.09) *¥		
Mean n of loose stools, day 4		Not statistically significant: 0.9±1.9 vs 0.9±2.0, MD: 0, 95%CI [-1.00;1.00] (p=1.00) *¥		
Mean n of loose stools, day 5		Not statistically significant: 0.6±1.3 vs 0.6±1.4, MD: 0, 95%CI [-0.70;0.70] (p=1.00) *¥		
Zinc-fortified-WHO ORS				
Mean diarrhoea duration (days)	Zinc-fortified-WHO ORS vs WHO ORS	Statistically significant: 2.98±0.92 vs 3.67±1.63 MD: -0.69, 95%CI [-1.17;-0.21] (p=0.009) * *In favour of zinc-fortified-WHO ORS*	1, 60 vs 57 §	Gregorio, 2007
Duration of diarrhoea < 4 days		Statistically significant: 54/59 vs 43/57 RR: 1.21, 95%CI [1.03;1.43] (p=0.02) * *In favour of zinc-fortified-WHO ORS*	1, 59 vs 57 §	
Duration of diarrhoea since enrolment >24 h		Not statistically significant: 103/248 vs 101/252 § RR: 1.05, 95CI% [0.93;1.19]	1, 248 vs 252	Wadhwa, 2011
Duration of diarrhoea since enrolment >48 h		Not statistically significant: 167/248 vs 161/252 § RR: 1.02, 95%CI [0.83;1.27] ¥		
Duration of diarrhoea since enrolment >72 h		Not statistically significant: 55/248 vs 59/252 § RR: 0.94, 95%CI [0.69;1.30] ¥		
Unscheduled IVF		Not statistically significant: 19/248 vs 24/252 § RR: 0.80, 95%CI [0.45;1.43] ¥		

Vomiting in first 24 h		Not statistically significant: 112/248 vs 104/25 § RR:21.09, 95%CI [0.89;1.34] ¥		
Mean diarrhoea frequency	Zinc syrup plus ORS vs Placebo plus ORS	Statistically significant: 4.5±2.3 vs 5.2±2.1 MD: -0.7, 95%CI [-1.22;-0.18] (p=0.004)* *In favour of ORS plus zinc*	1, 150 vs 156 §	Karamyyar, 2013
Hospitalisation duration		Statistically significant: 2.5±0.7 vs 3.3±0.8 MD: -0.8, 95%CI [-0.97;-0.63] (p<0.001)* *In favour of ORS plus zinc*		

* Calculations done by the reviewer(s) using Review Manager software
¥ Imprecision (large variability of results)
§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Gregorio, 2007	No block randomization with use of sealed envelopes	No, double blind	No	No	
Karamyyar, 2013	No, computerized software	No double blind	No	No	
Tran, 2015	No, randomization was performed by a computer program.	No, double blind	No	No	
Wadhwa, 2011	No, permuted blocks of 6	No, double blind	No	No	

Level of evidence

	High [A]	Downgrading due to
Limitations of study design	0	
Imprecision	-1	Large variability of results and limited sample sizes or low number of events.
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Moderate [B]**	

Conclusion(s)	Zinc-fortified rice ORS There is limited evidence neither in favour of the intervention nor the control: A statistically significant decrease of diarrhoea duration or mean loose stools (2-5 days), using zinc-fortified-rice-based ORS compared to no-zinc-fortified ORS, could not be demonstrated. It was shown that zinc-fortified-rice based ORS did not result in a statistically significant difference of outcome mean loose stools at day 1- day 5 and median diarrhoea duration compared to no zinc fortified ORS (Tran 2015). Evidence is of moderate quality and results of this study are imprecise due to limited sample size and large variability of results. Zinc-fortified WHO ORS There is evidence in favour of zinc-fortified WHO ORS. It was shown that zinc fortified ORS resulted in a statistically significant decrease of mean diarrhoea frequency, hospitalisation duration, mean diarrhoea duration, and duration of diarrhoea less than 4 days, compared to standard WHO ORS (Gregorio 2007 and Karamyyar 2013). No effect of duration of diarrhoea since enrolment longer than 24, 48 or 72 hours could be demonstrated (Wadhwa 2011). Evidence is of moderate quality and results of this study are imprecise due to limited sample size, low number of events and/or large variability of results.
Reference(s)	**Articles** Gregorio GV, Dans LF, Cordero CP, Panelo CA. *Zinc supplementation reduced cost and duration of acute diarrhea in children.* J Clin Epidemiol 2007; 60(6):560-566. Karamyyar M, Gheibi S, Noroozi M, Kord VA. *Therapeutic effects of oral zinc supplementation on acute watery diarrhea with moderate dehydration: a double-blind randomized clinical trial.* Iran J Med Sci. 2013;38(2): 93-99. Tran CD, Hawkes J, Graham RD, Kitchen JL, Symonds EL, Davidson GP et al. *Zinc-fortified oral rehydration solution improved intestinal permeability and small intestinal mucosal recovery*. Clin Pediatr (Phila) 2015; 54(7):676-682. Wadhwa N, Natchu UC, Sommerfelt H, Strand TA, Kapoor V, Saini S et al. *ORS containing zinc does not reduce duration or stool volume of acute diarrhea in hospitalized children*. J Pediatr Gastroenterol Nutr 2011; 53(2):161-167.

Diarrhoea – Home-made Oral rehydration solution (ORS) – Effectiveness (First Aid)

Question (PICO)	In people with diarrhea (P) is intake of home-made (I) compared to standard ORS effective to influence survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of the symptoms (O)?
Search Strategy	Databases **Cochrane:** (systematic reviews and controlled trials) using the following search strategy: 1. [mh diarrhea] OR [mh dehydration] OR diarr*:ti,ab,kw OR dehydrat*:ti,ab,kw 2. [mh "fluid therapy"] OR rehydr*:ti,ab,kw OR ORS:ti,ab,kw OR hydrat*:ti,ab,kw 3. "home prepared":ti,ab,kw OR "home made":ti,ab,kw OR "home care":ti,ab,kw 4. 1-3 AND **Pubmed:** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Diarrhea"[Mesh] OR "Dehydration"[Mesh] OR diarr*[TIAB] OR dehydrat*[TIAB] 2. "Fluid Therapy"[Mesh] OR "rehydration solutions"[Mesh] OR ORS[TIAB] OR hydrat*[TIAB] OR rehydr*[TIAB] OR ORT[TIAB] OR oral rehydration solution*[TIAB] OR oral rehydration therap*[TIAB] 3. "home prepared"[TIAB] OR "home made"[TIAB] OR "home management"[TIAB] OR "Home Nursing"[Mesh] OR "home care"[TIAB] 4. 1-3 AND **Embase:** (via Embase.com interface) using the following search strategy:

	1. 'diarrhea'/exp OR 'dehydration'/exp OR diarrhea:ab,ti OR diarrhoea:ab,ti OR dehydration:ab,ti 2. 'oral rehydration therapy'/exp OR 'oral rehydration solution'/exp OR ORS:ab,ti OR hydrat*:ab,ti OR rehydr*:ab,ti OR ORT:ab,ti OR oral rehydration solution*ab,ti OR oral rehydration therap*:ab,ti 3. 'home prepared':ab,ti OR 'home made':ab,ti OR 'home management':ab,ti OR 'home care'/exp OR 'home care':ab,ti 4. 1—3 AND
Search date	21 June 2016
In/Exclusion criteria	**Population**: Include: people with acute diarrhoea of all ages. **Intervention**: Include: Home-made ORS. Exclude: all other ORS. **Comparison:** Include: Home-made ORS. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion(s)	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	Not applicable

Diarrhoea – Home-made Oral rehydration solution (ORS) - Feasibility (First Aid)

Question (PICO)	Is it feasible for people with diarrhoea in a home-setting (P) to correctly prepare (O) one type of home-made ORS (I) compared to another type of home-made ORS (C)?
Search Strategy	Databases **Cochrane:** (systematic reviews and controlled trials) using the following search strategy: 1. [mh diarrhea] OR [mh dehydration] OR diarr*:ti,ab,kw OR dehydrat*:ti,ab,kw 2. [mh "fluid therapy"] OR rehydr*:ti,ab,kw OR ORS:ti,ab,kw OR hydrat*:ti,ab,kw

	3. "home prepared":ti,ab,kw OR "home made":ti,ab,kw OR "home care":ti,ab,kw 4. 1-3 AND **Pubmed:** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Diarrhea"[Mesh] OR "Dehydration"[Mesh] OR diarr*[TIAB] OR dehydrat*[TIAB] 2. "Fluid Therapy"[Mesh] OR "rehydration solutions"[Mesh] OR ORS[TIAB] OR hydrat*[TIAB] OR rehydr*[TIAB] OR ORT[TIAB] OR oral rehydration solution*[TIAB] OR oral rehydration therap*[TIAB] 3. "home prepared"[TIAB] OR "home made"[TIAB] OR "home management"[TIAB] OR "Home Nursing"[Mesh] OR "home care"[TIAB] 4. 1-3 AND **Embase:** (via Embase.com interface) using the following search strategy: 1. 'diarrhea'/exp OR 'dehydration'/exp OR diarrhea:ab,ti OR diarrhoea:ab,ti OR dehydration:ab,ti 2. 'oral rehydration therapy'/exp OR 'oral rehydration solution'/exp OR ORS:ab,ti OR hydrat*:ab,ti OR rehydr*:ab,ti OR ORT:ab,ti OR oral rehydration solution*ab,ti OR oral rehydration therap*:ab,ti 3. 'home prepared':ab,ti OR 'home made':ab,ti OR 'home management':ab,ti OR 'home care'/exp OR 'home care':ab,ti 4. 1—3 AND
Search date	21 June 2016
In/Exclusion criteria	**Population**: Include: people with acute diarrhoea of all ages. **Intervention**: Include: One type of home-made ORS, prepared by laypeople. **Comparison:** Include: Another type of home-made ORS, or standard ORS in packages, prepared by laypeople. **Outcome**: Include: correctness (i.e. safe (between 51 mmol/l-120 mmol/l) range of sodium concentration) of preparation of ORS, measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline). **Publication year**: Include: all years.

Characteristics of included studies

Author, year Country	Study design	Population	Comparison	Remarks
Kenya, 2001 Switzerland	Experimental: Randomized controlled trial	Mothers of 6180 children were trained to prepare and administer the prepared maize and glucose ORS to children aged 3-59 months old during episodes of diarrhoea in a rural district of Western Kenya.	Packets containing standard glucose reconstituted with water (= glucose ORS) vs packets with pre-weighed maize (60 g) and salt (5 g) reconstituted with	

			clear water (= maize salt ORS). Mothers were taught to take 1100 ml clean water and to mix it with the pre-weighed flour provided and to stir thoroughly. The mixture was then heated with continuous stirring until the mixture boiled to a homogenous solution. After allowing the solution to cool, 5 g common salt was added (provided in a smaller packet) and stirred thoroughly until it dissolved. For the glucose ORS: mothers were taught to take 1 litre of clean drinking water and to add one packet of glucose and to mix thoroughly.	

Synthesis of findings

Outcome	Comparison/Risk factor	Effect Size	#studies, # participants	Reference
Home-reconstituted ORS with sodium level <50 (mmol/l)	Glucose home-reconstituted ORS vs maize and salt home-reconstituted ORS	Not statistically significant: 7/174 vs 12/148 § OR: 0.48, 95%CI [0.18;1.24] (p=0.16)	1, 174 vs 148	Kenya, 2001
Home-reconstituted ORS with sodium level 51-120 (mmol/l)		Statistically significant: 136/174 vs 134/148 OR: 0.37, 95%CI [0.19;0.72] (p=0.004) *In favour of maize and salt ORS*		
Home-reconstituted ORS with sodium level > 120 (mmol/l)		Statistically significant: 31/174 vs 2/148 OR: 15.83, 95%CI [3.72;67.38] (p=0.0001) *In favour of maize and salt ORS*		

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Kenya, 2001	No	Not reported, but not possible	No	No	Home water samples contained substantial amounts of salts which could unpredictably affect the final ORS composition.

§ Imprecision (low number of events)

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	Low number of events, lack of blinding, but blinding not possible.
Imprecision	0	
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Moderate [B]**	

Conclusion(s)	There is evidence in favour of maize and salt based home-made ORS. It was shown that maize and salt ORS resulted in a statistically significant decrease of ORS with sodium levels higher than 120 mmol/l, compared to glucose based ORS. In addition, It was shown that maize and salt ORS resulted in a statistically significant increase of ORS with sodium levels between 51-120 mmol/l (i.e. the safe range for sodium chloride levels), compared to glucose based ORS (Kenya 2001). A statistically significant increase of ORS with sodium levels lower than 50 mmol/l, using maize and salt ORS compared to glucose ORS could not be demonstrated (Kenya 2001). Evidence is of moderate quality.
Reference(s)	**Articles** Kenya PR, Muttunga JN, Mwenesi H, Molla AM, Bari A, Juma R, Were B, Molla A, Sharma PN. *Comparison of safety of glucose oral rehydration solution and maize oral rehydration therapy for home management of diarrhoea in Kenya.* J Trop. Pediatr. 2001, 47, 226-229.

Diarrhoea & dehydration – Contact (risk factor)

Question (PICO)	In humans (P), is having contact with raw meat, people or children with diarrhoea, pets, farm animals or children (I) a risk factor for diarrhoea or dehydration (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search term: 1. [mh "Diarrhea"] OR [mh "Dehydration"] OR diarrhoea:ti,ab OR diarrhoea:ti,ab OR diarrhea:ti,ab 2. [mh "Risk factors"] OR (risk NEXT factor*):ti,ab 3. 1-2 AND **MEDLINE** (via PubMed interface) for guidelines and systematic reviews using the following search strategy: 1. "Diarrhea"[Mesh] OR "Dehydration"[Mesh] OR diarrhea[TIAB] OR diarrhoea[TIAB] OR dehydration[TIAB]

	2. "Food handling"[Mesh] OR "Food Contamination"[Mesh] OR "Hygiene"[Mesh] OR "Drinking"[Mesh] OR "Eating"[Mesh] OR "Food"[Mesh] OR kitchen[TIAB] OR hygiene[TIAB] OR drinking[TIAB] OR eating[TIAB] OR bottle[TIAB] OR spicy[TIAB] OR spices[TIAB] OR coffee[TIAB] OR raw[TIAB] 3. "Risk factors"[Mesh] OR risk factor*[TIAB] 4. "Epidemiologic Studies"[Mesh] OR "case-control"[TIAB] OR ((case[TIAB] OR cases[TIAB]) AND (control[TIAB] OR controls[TIAB])) OR "cohort study"[TIAB] OR "cohort analysis"[TIAB] OR "follow-up study"[TIAB] OR "observational study"[TIAB] OR "longitudinal"[TIAB] OR "retrospective"[TIAB] 5. 1-4 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'diarrhea'/exp OR 'dehydration'/exp OR diarrhea:ab,ti OR diarrhoea:ab,ti OR dehydration:ab,ti 2. 'food handling'/exp OR 'food contamination'/exp OR 'hygiene'/exp OR 'drinking'/exp OR 'eating'/exp OR 'food'/exp OR kitchen:ab,ti OR hygiene:ab,ti OR drinking:ab,ti OR eating:ab,ti OR bottle:ab,ti OR spicy:ab,ti OR spices:ab,ti OR coffee:ab,ti OR raw:ab,ti 3. 'risk factor'/exp OR (risk NEXT/1 factor*):ab,ti 4. 'cohort analysis'/exp OR 'case-control':ab:ti OR ((case:ab:ti OR cases:ab:ti) AND (control:ab:ti OR controls:ab:ti)) OR 'cohort study':ab:ti OR 'cohort analysis':ab:ti OR 'follow-up study':ab:ti OR 'observational study':ab:ti OR 'longitudinal':ab:ti OR 'retrospective':ab:ti 5. 1-4 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in MEDLINE (via PubMed interface).
Search date	24 August 2015
In/Exclusion criteria	**Population**: Include: people in developed countries (according to definition of Worldbank and statistics of the International Statistical Institute); travellers from developed countries (also travelling to developing countries); cases have diarrhoea from various origin (infection with *Campylobacter*, *Cryptosporidium*, *Escherichia coli* 0157:H7, *Salmonella*, *Giardia* or origin of diarrhoea not mentioned; remark: since a *Giardia* infection can occur asymptomatic, only studies were included where presence of diarrhoea was explicitly mentioned), but have no other illnesses; controls are healthy; Exclude: neonates; inhabitants of a region where an epidemic or outbreaks occurs; people residing in refugee camps or a disaster setting; victims of nosocomial infections **Intervention**: Include: modifiable, proximal risk factor with a potential immediate implication for practice that results in primary prevention at the household or community level. Risk factors related to healthy persons; risk factors that are relevant for European inhabitants or travellers; Exclude: risk factors that do not precede the outcome; risk factors that are common sense; risk factors concerning water purification, hand washing and latrine use (since these are covered in other PICO's); risk factors concerning breastfeeding or the use of concentrated infant formula (not proximal/not always modifiable); travelling as such as a risk factor was excluded (not modifiable), however specific risk factors relevant during travelling were included **Outcome**: Include: (risk of) diarrhoea, risk of *Salmonella*/*Campylobacter*/*Cryptosporidium*/*E. coli* 0157:H7 infection; dehydration; only data from multivariate analysis were extracted, i.e. data that were adjusted for confounding variables; Exclude: (risk of) hospital admission, chronic diarrhoea, data from univariate analysis (unadjusted) **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An observational study: inclusion in case of one of the following study types: cohort and case-control study (taking into account confounding variables at the analysis phase),

	controlled before and after study or controlled interrupted time series, and the data are available. Exclude: observational studies not taking into account confounding variables at the analysis phase, conference abstracts, case series, cross-sectional studies (studies collecting information concerning type of car and injury in health insurance companies), animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline)

Characteristics of included studies

Author, year, Country	Study design	Population	Risk factors	Remarks
Ethelberg, 2006, Denmark	Observational: case-control study	Cases (n=422): children less than 5 years of age with a stool sample submitted for examination for infectious gastroenteritis Controls (n=866): healthy controls selected from the background population using a population register, matched for sex, week of birth and county of residence	Multiple risk factors: prior diagnosis of common childhood diseases other than gastroenteritis, medication, contact with other symptomatic persons, foreign travel, contact with animals, playing in water at various locations, consumption of different types of milk and water, daycare, whether the family bought organic products, and socioeconomic status of the parents	Risk factors were determined in an interview. A multivariate logistic regression analysis was performed.
Fullerton, 2007, USA	Observational: case-control study	Cases (n=123): Infants 0–6 months of age with *Campylobacter* infection Controls (n=928): were randomly selected from birth registries in each state, matched to cases by age and state of residence	Multiple risk factors: environmental exposures (household exposures, child care settings, animals, petting zoos and farms and international travel) and food exposures (breast-feeding, formula, water and solid food)	A standard questionnaire was administered by telephone to parents/ guardians of cases and controls. Multivariable unconditional logistic regression models were applied.
Holton, 1999, Canada	Observational: case-control study	Cases (n=100): persons with gastrointestinal symptoms and a positive stool culture for *E. coli* 0157:H7 (median age: 17.5 years) Controls (n=200): Two neighbourhood residents matched to each case by age	Multiple risk factors: contact with persons suffering from diarrheal illness; consumption, handling and preparation of ground beef and ground beef patties; consumption of other beef cuts and ground meats; consumption of other types of foods; and	Cases and controls were interviewed face-to-face to obtain information on potential risk factors for infection and health outcomes. A multivariable analysis was performed.

		and sex were recruited as controls according to a standardized protocol Infants under one year of age were excluded.	presence in settings where ground beef was eaten	
Jones, 2006, USA	Observational: case-control study	Cases (n=442): infants < 1 year with from whom any serotype of *Salmonella* other than Typhi was isolated from a clinical specimen Controls (n=928): identified through birth registries or published birth announcements, and matched by age	Multiple risk factors: water source, formula types, various foods and manner of preparation, previous antibiotic use, and animal exposures	An extensive questionnaire was administered by telephone to the parents or guardians of the subjects and controls. A multivariable regression analysis was performed.
Kassenborg, 2004, USA	Observational: case-control study	Cases (n=196): patients with non–outbreak-related diarrheal illness who had O157 isolated from their stool samples (*E. coli* 0157:H7) (median age: 12 years) Controls (n=372): healthy persons matched by age and telephone number exchange	Multiple risk factors: antibiotic and antacid use, any immune-compromising conditions or chronic illnesses that existed in the 4 weeks before the case patient's onset of illness, travel, child day care, exposure to farms and cows, meathandling practices, sources of drinking water and ground beef, and consumption of fruits, vegetables, and meats during the 5-day period before the case patient's date of disease onset	Case patients were interviewed within 21 days of their stool sample collection date, and controls were interviewed within 7 days after the patient's interview. A multivariate analysis was performed.
Kist, 2000, Germany	Observational: case-control study	Cases (n=965): diarrhoeic and/or febrile illness and isolation of *Salmonella* Enteritidis (n=790) or non-Enteritidis Salmonella (n=175) in their stool Controls (n=256): healthy individuals, called by phone in the Freiburg study area (people reporting symptoms compatible with enteric infection were excluded); matching by age group and sex was done	Multiple risk factors: place of residence, foreign travel during 2 weeks before onset of symptoms, preceding (2 weeks) fever or diarrhoea in contact persons, prior (1 month) consumption of antacids or antimicrobials, consumption of various food during 48 h before onset of symptoms, and contact with domestic and farm animals and pets	Cases were interviewed by their physician; controls were interviewed via telephone. A multivariable logistic regression analysis was performed.
Robertson, 2002, Australia	Observational: case-control study	Cases (n=134): people having having *Cryptosporidium*	Multiple risk factors: education level, employment, the	A computer assisted

		oocysts detected in a faecal specimen by an accredited pathology laboratory, the onset of any diarrhoea or vomiting within 8 weeks before the administration of questionnaire, residence in a household with a fixed telephone connection and the ability to speak English (median age: 11 years) Controls (n=536): people not having diarrhoea or vomiting in the 2 weeks before the onset of the matching case's illness, residence in a household with a fixed telephone connection and the ability to speak English	consumption of tap water, the consumption of particular food groups, recreational water activities, the presence of immunological impairment, the consumption of regular medication, contact with persons who may pose a risk of cryptosporidiosis, animal contact, rural or overseas travel and exposure to child-care or breast feeding.	telephone questionnaire was used. A stratified Cox proportional hazard regression analysis was performed. Data were collected in Melbourne and Adelaide. Only data that were consistently significant (or not) at both sites were extracted. Only Melbourne data were extracted.
Schorr, 1994, Switzerland	Observational: case-control study	Cases (n=167): people ≥ 15 years and < 65 years with gastrointestinal symptoms (mostly diarrhea) and whose stool specimen was submitted for culture to one of the participating laboratories yielded *Campylobacter* Controls (n=282): people who had no diarrheal illness within two weeks before completing the control questionnaire, matched for sex	Multiple risk factors: information on food preferences, and contained questions on a number of specific food items consumed in the five days preceding onset of symptoms, and further factors considered to be potential risk factors for the disease under study (travel abroad, water consumption, pet animals, predisposing factors like use of antacids and antibiotics or serious medical conditions)	Risk factors were assessed through questionnaires. A multivariate analysis was performed.
Valderrama, 2009, USA	Observational: case-control study	Cases (n=45): Colorado resident who had a positive *Cryptosporidium* laboratory stool test (median age: 19 years) Controls (n=89):a Colorado resident who had experienced no gastrointestinal symptoms, matched by age and geographic area	Multiple risk factors: food and water consumption, recreational water exposure, child care and household exposures, farm and animal contact, person-to-person contact, and travel history during the exposure period as well as basic demographics	A standardized questionnaire was developed and administered by telephone. Case-patients and corresponding matched controls were asked about possible exposures during the 2 weeks prior

				to the case-patient's onset of symptoms. A multivariable analysis was performed.

Synthesis of findings

Outcome	Risk factor	Effect Size	#studies, # participants	Reference
Contact with raw meat				
Risk of non-typhimurium *Salmonella*	Rode in shopping cart next to meat or poultry vs not	Statistically significant: OR: 3.2, 95%CI [2.1;5.1] (p<0.05) £† *With harm for riding in a shopping cart next to meat or poultry*	1, 442 vs 928	Jones, 2006
Risk of *Campylobacter* infection		Statistically significant: 15/116 vs 54/905 § OR: 2.2, 95%CI [1.1;4.6] (p<0.05) *With harm for riding in a shopping cart next to meet or poultry*	1, 123 vs 928	Fullerton, 2007
Pets/animals at home				
Risk of *Salmonella* infection	Having puppies, kittens or turtles vs not	Statistically significant: OR: 6.8 (p=0.002) £† *With harm for having puppies, kittens or turtles*	1, 965 vs 790	Kist, 2000
Risk of non-typhimurium *Salmonella*	Reptile exposure vs not	Statistically significant: OR: 5.2, 95%CI [3.4;7.9] (p<0.05) £† *With harm for reptile exposure*	1, 442 vs 928	Jones, 2006
Risk of *Cryptosporidium* infection	Animal contact at home vs not	Statistically significant: OR: 0.6, 95%CI [0.4;0.8] (p<0.05) £† *With benefit for animal contact at home*	1, 134 vs 536	Robertson, 2002
Risk of *Campylobacter* infection	Keeping a pet vs not	Not statistically significant: OR: 0.9, 95%CI [0.5;1.6] ¥ (p<0.05) £†	1, 167 vs 282	Schorr, 1994
Other people/animals with diarrhoea/illness				
Risk of *Cryptosporidium* infection	Children < 6 yr at home with diarrhoea vs not	Statistically significant: OR: 7.4, 95%CI [4.0;13.8] (p<0.05) £† *With harm for children < 6 yr at home with diarrhoea*	1, 134 vs 536	Robertson, 2002
Risk of *Cryptosporidium* infection	Persons > 5 yr at home with diarrhoea vs not	Statistically significant: OR: 1.8, 95%CI [1.1;2.9] (p<0.05) £† *With harm for persons > 5 yr at home with diarrhoea*	1, 134 vs 536	Robertson, 2002
Risk of *E. coli* 0157:H7 infection	Contact with household member with diarrhoeal illness vs not	Statistically significant: OR: 2.55, 95%CI [1.07;6.20] (p=0.0164) £†	1, 100 vs 200	Holton, 1999

		With harm for contact with household member with diarrhoeal disease		
Risk of *E. coli* 0157:H7 infection	Contact with non-household member with diarrhoeal illness vs not	Statistically significant: OR: 6.29, 95%CI [1.63;35.35] (p=0.0021) £† *With harm for contact with non-household members with diarrhoeal disease*	1, 100 vs 200	Holton, 1999
Risk of diarrhoea	Contact with ill person past 2 weeks vs not	Statistically significant: OR: 2.19, 95%CI [1.64;2.92] (p<0.05) £† *With harm for contact with an ill person the past 2 weeks*	1, 422 vs 866	Ethelberg, 2006
Risk of diarrhoea	Dog had diarrhoea vs not	Statistically significant: OR: 2.02, 95%CI [1.03;3.98] (p<0.05) £† *With harm for dog having diarrhoea*	1, 422 vs 866	Ethelberg, 2006
Risk of *Campylobacter* infection	Having a pet with diarrhoea in the home vs not	Statistically significant: 9/123 vs 17/928 § OR: 5.3, 95%CI [1.8;15.5] (p<0.05) *With harm for having a pet with diarrhoea in the home*	1, 123 vs 928	Fullerton, 2007
Children/day care				
Risk of *Cryptosporidium* infection	Contact with child in child care or in diapers vs not	Statistically significant: 31/45 vs 40/89 § OR: 3.8, 95%CI [1.5;9.6] (p<0.05) *With harm for contact with a child in child care or diapers*	1, 45 vs 89	Valderrama, 2009
Risk of non-typhimurium *Salmonella*	Attended day care centre with another child vs not	Statistically significant: OR: 4.4, 95%CI [1.8;10.7] (p<0.05) £† *With harm for attending a day care centre with another child*	1, 442 vs 928	Jones, 2006
Risk of *Campylobacter* infection	Attending child care vs not	Not statistically significant: 23/122 vs 211/926 § OR: 0.7, 95%CI [0.4;1.2] (p>0.05) ¥	1, 123 vs 928	Fullerton, 2007
Risk of *E. coli* 0157:H7 infection	Attendance at day care vs not	Not statistically significant: OR: 2.87, 95%CI [0.87;11.00] ¥ (p=0.0461) £†	1, 100 vs 200	Holton, 1999
Risk of diarrhoea	Using private day care provider vs not	Statistically significant: OR: 1.33, 95%CI [1.01;1.75] (p<0.05) £† *With harm for using a rivate day care provider*	1, 422 vs 866	Ethelberg, 2006
Farm visit/contact with farm animals				
Risk of diarrhoea	Contact with cows vs not	Statistically significant: OR: 0.50, 95%CI [0.27;0.93] (p<0.05) £†	1, 422 vs 866	Ethelberg, 2006

		With benefit for contact with cows		
Risk of non-typhimurium *Salmonella*	Farm animal contact vs not	Not statistically significant: OR: 2.1, 95%CI [0.5;9.3] ¥ (p>0.05) £†	1, 442 vs 928	Jones, 2006
Risk of *Campylobacter* infection	Visiting or living on a farm vs not	Statistically significant: 25/122 vs 41/923 § OR: 4.1, 95%CI [1.9;8.9] (p<0.05) *With harm for visiting or living on a farm*	1, 123 vs 928	Fullerton, 2007
Risk of *E. coli* 0157:H7 infection	Persons > 6 yrs: Visited farm with cows vs not	Statistically significant: 14/193 vs 5/368 § OR: 10, 95%CI [1.8;53] (p=0.007) *With harm for persons > 6 yr visiting a farm with cows*	1, 193 vs 368	Kassenborg, 2004
Risk of *E. coli* 0157:H7 infection	Persons < 6 yrs: Lived on farm or visited farm vs not	Statistically significant: 17/195 vs 8/369 § OR: 5.2, 95%CI [1.3;22] (p=0.02) *With harm for persons < 6 yrs living on a farm or visiting a farm*	1, 195 vs 369	Kassenborg, 2004
Risk of *Cryptosporidium* infection	Calf contact away from home vs not	Statistically significant: OR: 2.9, 95%CI [1.5;5.7] (p<0.05) £† *With harm for calf contact away from home*	1, 134 vs 536	Robertson, 2002

£ No raw data available
§ Imprecision (low number of events)
† Imprecision (lack of data)
¥ Imprecision (large variability of results)

Quality of evidence

Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations
Ethelberg, 2006	No (matched cases and controls)	No	No (multivariable analysis)	No	
Fullerton, 2007	No (matched cases and controls)	No	No (multivariable analysis)	No	
Holton, 1999	No (matched cases and controls)	No	No (multivariable analysis)	No	
Jones, 2006	No (matched cases and controls)	No	No (multivariable analysis)	No	
Kassenborg, 2004	No (matched cases and controls)	No	No (multivariable analysis)	No	
Kist, 2000	No (matched cases and controls)	Yes, possible differences in how risk factors were assessed	No (multivariable analysis)	No	

		in cases and controls: cases were interviewed by their physician; controls were interviewed via telephone			
Robertson, 2002	No (matched cases and controls)	No	No (multivariable analysis)	No	
Schorr, 1994	No (matched cases and controls)	No	No (multivariable analysis)	No	
Valderrama, 2009	No (matched cases and controls)	No	No (multivariable analysis)	No	

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Low number of events, lack of data or large variability in results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low[D]**	

Conclusion	**Contact with raw meat** It was shown that the following risk factor resulted in a statistically significant increased risk of *Salmonella*/*Campylobacter* infection: riding in a shopping cart next to meat or poultry (Jones 2006, Fullerton 2007). Evidence is of very low quality and results cannot be considered precise due to limited sample size, lack of data and large variability of results. **Pets/animals at home** There is conflicting evidence concerning having pets/animals at home. It was shown that having puppies/kittens/turtles or reptile exposure resulted in a statistically significant increased risk of *Salmonella* infection (Kist 2000, Jones 2006). On the other hand it was shown that animal contact at home resulted in a statistically significant decreased risk of *Cryptosporidium* infection (Robertson 2002). In another study a statistically significant difference in the risk of *Campylobacter* infection in case of keeping a pet could not be demonstrated (Schorr 1994). Evidence is of very low quality and results cannot be considered precise due to limited sample size, lack of data and large variability of results. **Other people/animals with diarrhoea/illness** It was shown that the following risk factors resulted in a statistically significant increased risk of *Campylobacter*/*Cryptosporidium*/*E. coli* 0157:H7 infection or risk of diarrhoea: children < 6 yr at home with diarrhoea, persons > 5 yr at home with diarrhoea, contact with household member with diarrhoeal illness, contact with non-household member with diarrhoeal illness, contact with ill person past 2 weeks, dog had diarrhoea, having a pet with diarrhoea (Fullerton 2007, Robertson 2002, Holton 1999, Ethelberg 2006). Evidence is of very low quality and results cannot be considered precise due to limited sample size, lack of data and large variability of results. **Children/day care** It was shown that the following risk factors resulted in a statistically significant increased risk of *Salmonella*/*Cryptosporidium* infection or risk of diarrhoea: contact with child in child care or diapers, attending day care centre with another child and using private day care provider (Ethelberg 2006, Valderrama 2009, Jones 2006). A statistically significant increased risk of *Campylobacter* or *E. coli* 0157:H7 infection in case of attendance at day care could not be demonstrated in two smaller studies (Fullerton 2007, Holton 1999). Evidence is of very low quality and results cannot be considered precise due to limited sample size, lack of data and large variability of results. **Farm visit/contact with farm animals** There is conflicting evidence concerning a farm visit/contact with farm animals. It was shown that visiting or living on a farm, visiting a farm with cows (for persons > 6 yrs), and calf contact away from home resulted in a statistically significant increased risk of *Campylobacter*/*E. coli* 0157:H7/*Cryptosporidium* infection (Fullerton 2007, Kassenborg 2004, Robertson 2002). On the other hand it was shown that contact with cows resulted in a statistically significant decreased risk of diarrhoea (Ethelberg 2006). In another study a statistically significant difference in the risk of Salmonella infection in case of farm animal contact could not be demonstrated (Jones 2006). Evidence is of very low quality and results cannot be considered precise due to limited sample size, lack of data and large variability of results.
Reference(s)	**Articles** Ethelberg S, Olesen B, Neimann J, Schiellerup P, Helms M, Jensen C, Böttiger B, Olsen KE, Scheutz F, Gerner-Smidt P, Mølbak K. *Risk factors for diarrhea among children in an industrialized country*. ***Epidemiology*** 2006, **17(**1): 24-30 Fullerton KE, Ingram LA, Jones TF, Anderson BJ, McCarthy PV, Hurd S, Shiferaw B, Vugia D, Haubert N, Hayes T, Wedel S, Scallan E, Henao O, Angulo FJ. *Sporadic campylobacter infection in infants: a population-based surveillance case-control study*. Pediatr Infect Dis J 2007, 26(1):19-24

	Holton D, Wilson J, Ellis A, Haldane D, April N, Grimsrud K, Friesen B, Spika J. *A Canadian multicentre case-control study of sporadic Escherichia coli 0157:H7 infection*. Can J Infect Dis 1999, 10(2):117-21 Jones TF, Ingram LA, Fullerton KE, Marcus R, Anderson BJ, McCarthy PV, Vugia D, Shiferaw B, Haubert N, Wedel S, Angulo FJ. *A case-control study of the epidemiology of sporadic Salmonella infection in infants*. ***Pediatrics*** 2006, **118(**6): 2380-238 Kassenborg HD, Hedberg CW, Hoekstra M, Evans MC, Chin AE, Marcus R, Vugia DJ, Smith K, Ahuja SD, Slutsker L, Griffin PM. *Farm visits and undercooked hamburgers as major risk factors for sporadic Escherichia coli O157:H7 infection: Data from a case-control study in 5 FoodNet sites*. Clin Infect Dis 2004, 8 Suppl 3:S271-8 Kist MJ, Freitag S. *Serovar specific risk factors and clinical features of Salmonella enterica ssp. enterica serovar Enteritidis: a study in South-West Germany*. Epidemiol Infect 2000, 124(3):383-92 Robertson B, Sinclair MI, Forbes AB, Veitch M, Kirk M, Cunliffe D, Willis J, Fairley CK. *Case-control studies of sporadic cryptosporidiosis in Melbourne and Adelaide, Australia*. Epidemiol Infect 2002, 128(3):419-31 Schorr D, Schmid H, Rieder HL, Baumgartner A, Vorkauf H, Burnens A. *Risk factors for Campylobacter enteritis in Switzerland*. Zentralbl Hyg Umweltmed 1994, 196(4):327-37 Valderrama AL, Hlavsa MC, Cronquist A, Cosgrove S, Johnston SP, Roberts JM, Stock ML, Xiao L, Xavier K, Beach MJ. *Multiple risk factors associated with a large statewide increase in cryptosporidiosis*. Epidemiol Infect 2009, 137(12):1781-8

Diarrhoea & dehydration – drinking and swimming (Risk factor)

Question (PICO)	In humans (P), is drinking certain fluids/swimming (I) a risk factor for diarrhoea or dehydration (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search term: 1. [mh "Diarrhea"] OR [mh "Dehydration"] OR diarrhoea:ti,ab OR diarrhoea:ti,ab OR diarrhea:ti,ab 2. [mh "Risk factors"] OR (risk NEXT factor*):ti,ab 3. 1-2 AND **MEDLINE** (via PubMed interface) for guidelines and systematic reviews using the following search strategy: 1. "Diarrhea"[Mesh] OR "Dehydration"[Mesh] OR diarrhea[TIAB] OR diarrhoea[TIAB] OR dehydration[TIAB] 2. "Food handling"[Mesh] OR "Food Contamination"[Mesh] OR "Hygiene"[Mesh] OR "Drinking"[Mesh] OR "Eating"[Mesh] OR "Food"[Mesh] OR kitchen[TIAB] OR hygiene[TIAB] OR drinking[TIAB] OR eating[TIAB] OR bottle[TIAB] OR spicy[TIAB] OR spices[TIAB] OR coffee[TIAB] OR raw[TIAB] 3. "Risk factors"[Mesh] OR risk factor*[TIAB] 4. "Epidemiologic Studies"[Mesh] OR "case-control"[TIAB] OR ((case[TIAB] OR cases[TIAB]) AND (control[TIAB] OR controls[TIAB)) OR "cohort study"[TIAB] OR "cohort analysis"[TIAB] OR "follow-up study"[TIAB] OR "observational study"[TIAB] OR "longitudinal"[TIAB] OR "retrospective"[TIAB] 5. 1-4 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'diarrhea'/exp OR 'dehydration'/exp OR diarrhea:ab,ti OR diarrhoea:ab,ti OR dehydration:ab,ti 2. 'food handling'/exp OR 'food contamination'/exp OR 'hygiene'/exp OR 'drinking'/exp OR 'eating'/exp OR 'food'/exp OR kitchen:ab,ti OR hygiene:ab,ti OR

	drinking:ab,ti OR eating:ab,ti OR bottle:ab,ti OR spicy:ab,ti OR spices:ab,ti OR coffee:ab,ti OR raw:ab,ti 3. 'risk factor'/exp OR (risk NEXT/1 factor*):ab,ti 4. 'cohort analysis'/exp OR 'case-control':ab:ti OR ((case:ab:ti OR cases:ab:ti) AND (control:ab:ti OR controls:ab:ti)) OR 'cohort study':ab:ti OR 'cohort analysis':ab:ti OR 'follow-up study':ab:ti OR 'observational study':ab:ti OR 'longitudinal':ab:ti OR 'retrospective':ab:ti 5. 1-4 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	24 August 2015
Inclusion/Exclusion criteria	**Population**: Include: people in developed countries (according to definition of Worldbank and statistics of the International Statistical Institute); travellers from developed countries (also travelling to developing countries); cases have diarrhoea from various origin (infection with *Campylobacter*, *Cryptosporidium*, *Escherichia coli* 0157:H7, *Salmonella*, *Giardia* or origin of diarrhoea not mentioned; remark: since a *Giardia* infection can occur asymptomatic, only studies were included where presence of diarrhoea was explicitly mentioned), but have no other illnesses; controls are healthy; Exclude: neonates; inhabitants of a region where an epidemic or outbreaks occurs; people residing in refugee camps or a disaster setting; victims of nosocomial infections **Intervention**: Include: modifiable, proximal risk factor with a potential immediate implication for practice that results in primary prevention at the household or community level. Risk factors related to healthy persons; risk factors that are relevant for European inhabitants or travellers; Exclude: risk factors that do not precede the outcome; risk factors that are common sense; risk factors concerning water purification, hand washing and latrine use (since these are covered in other PICO's); risk factors concerning breastfeeding or the use of concentrated infant formula (not proximal/not always modifiable); travelling as such as a risk factor was excluded (not modifiable), however specific risk factors relevant during travelling were included **Outcome**: Include: (risk of) diarrhoea, risk of *Salmonella*/*Campylobacter*/*Cryptosporidium*/*E. coli* 0157:H7 infection; dehydration; only data from multivariate analysis were extracted, i.e. data that were adjusted for confounding variables; Exclude: (risk of) hospital admission, chronic diarrhoea, data from univariate analysis (unadjusted) **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An observational study: inclusion in case of one of the following study types: cohort and case-control study (taking into account confounding variables at the analysis phase), controlled before and after study or controlled interrupted time series, and the data are available. Exclude: observational studies not taking into account confounding variables at the analysis phase, conference abstracts, case series, cross-sectional studies (studies collecting information concerning type of car and injury in health insurance companies), animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline)

Characteristics of included studies

Author, year, Country	Study design	Population	Risk factor	Remarks
Bassal, 2013, Israel	Observational: case-control study	Cases (n=263): culture-confirmed symptomatic patients diagnosed as having *Salmonella infantis* infection; 77 children ≤ 1 year; mean age of cases > 1 year: 22.8 years Controls (n=263): healthy controls through the Israeli Population Register, matched by gender, age and neighbourhood	Multiple risk factors: breastfeeding and formula use (for infants), contact with animals, and exposure to various food items (including eggs, poultry and meat, dairy products, fruits and vegetables), food handling and water consumption [only data on risk factors concerning drinking/drink water/swimming were extracted]	A comprehensive structured questionnaire was administered by telephone to all the cases and controls. A multivariable analysis was performed.
Pitzurra, 2010, Switzerland	Observational: cohort study	2800 travellers to a resource-limited country for the duration of 1 to 8 weeks. 962 travellers had travellers' diarrhoea, 1838 had not	Multiple risk factors: previous travel to the tropics, demographic data, body mass index, chronic diseases, confirmed allergies, and pretravel diarrhoea characteristics, adverse life events in the preceding 12 months, self-reported stress, smoking habits and alcohol consumption, perceived susceptibility to diarrhoea, attitudes towards diarrhoea (catering, adherence to 'cook it, boil it, peel it or forget it', tap water consumption) [only data on risk factors concerning drinking/drink water/swimming were extracted]	Upon signing an informed consent, the participants received two questionnaires. Q1 was collected immediately upon completion, while Q2 was to be returned in the first week after their return reminded either by mail or email; Q2 was similar to a diary. A multiple logistic regression model was used.
Schorr, 1994, Switzerland	Observational: case-control study	Cases (n=167): people ≥ 15 years and < 65 years with gastrointestinal symptoms (mostly diarrhoea) and whose stool specimen was submitted for culture to one of the participating laboratories yielded *Campylobacter* Controls (n=282): people who had no diarrheal illness within two weeks before completing the control	Multiple risk factors: information on food preferences, and contained questions on a number of specific food items consumed in the five days preceding onset of symptoms, and further factors considered to be potential risk factors for the disease under study (travel abroad, water consumption, pet animals, predisposing factors like use of antacids and	Risk factors were assessed through questionnaires. A multivariate analysis was performed.

		questionnaire, matched for sex	antibiotics or serious medical conditions) [only data on risk factors concerning drinking/drink water/swimming were extracted]	
Stuart, 2003, UK	Observational: case-control study	Cases (n=232): residents of the study area with a history of diarrhoea and *Giardia* cysts in their stool specimen seen by light microscopy (cases were most frequent in the 30- to 39-year age group) Controls (n=574): persons registered at the same general practice as patients, of the same gender, and in the same broad age band (0–5 years, 6–15 years, >16 years)	Multiple risk factors: recent illness, travel, water contact, water and food consumption (food history focusing on dairy produce, salads, fruit), and contact with animals, farms, and day nurseries [only data on risk factors concerning drinking/drink water/swimming were extracted]	Information from cases and controls was collected through interviews. A multivariable conditional logistic regression analysis was performed.
Valderrama, 2009, USA	Observational: case-control study	Cases (n=45): Colorado resident who had a positive *Cryptosporidium* laboratory stool test (median age: 19 years) Controls (n=89):a Colorado resident who had experienced no gastrointestinal symptoms, matched by age and geographic area	Multiple risk factors: food and water consumption, recreational water exposure, child care and household exposures, farm and animal contact, person-to-person contact, and travel history during the exposure period as well as basic demographics	A standardized questionnaire was developed and administered by telephone. Case-patients and corresponding matched controls were asked about possible exposures during the 2 weeks prior to the case-patient's onset of symptoms. A multivariable analysis was performed.

Synthesis of findings

Outcome	Risk factor	Effect Size	#studies, # participants	Reference
Swimming				
Risk of *Cryptosporidium* infection	Exposure to any recreational water vs not	Statistically significant: 29/45 vs 43/89 § OR: 4.6, 95%CI [1.4;14.6] ($p<0.05$) *with harm for exposure to any recreational water*	1, 45 vs 89	Valderrama, 2009

Risk of giardiasis	Recreational fresh water contact vs not	Statistically significant: OR: 5.5, 95% CI [1.9;15.9] (p=0.001) £† *with harm for recreational fresh water contact*	1, 232 vs 574	Stuart, 2003
	Swallowed water while swimming vs not	Statistically significant: OR: 6.2, 95% CI [2.3;16.6] (p<0.0001) £† *with harm for swallowed while swimming*		
Risk of *Campylobacter* infection	Using public swimming pool vs not	Not statistically significant: OR: 0.9, 95%CI [0.4;1.8] ¥ (p>0.05) £†	1, 167 vs 282	Schorr, 1994
Drinking tap water				
Risk of *Salmonella infantis* infection	Drank only tap water vs drank only bottled water or filtered water	Statistically significant: OR: 0.44, 95%CI [0.22;0.85] (p=0.02) £† *with benefit for drinking only tap water*	1, 263 vs 263	Bassal, 2013
Risk of giardiasis	Each additional glass of tap water consumed per day	Statistically significant: OR: 1.3, 95% CI [1.1;1.5] (p<0.0001) £† *with harm for each additional glass of tap water consumed per day*	1, 232 vs 574	Stuart, 2003
Risk of travellers' diarrhoea	Consuming tap water abroad vs not	Not statistically significant: OR: 0.88, 95%CI [0.62;1.25] ¥ (p>0.05) £†	1, 2565 (no information available about number of cases and controls)	Pitzurra, 2010

£ No raw data available
§ Imprecision (low number of events)
† Imprecision (lack of data)
¥ Imprecision (large variability of results)

Quality of evidence

Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations
Bassal, 2013	No (matched cases and controls)	No	No (multivariable analysis)	No	
Pitzurra, 2010	No (comparable demographics)	No	No (multivariable analysis)	No	
Schorr, 1994	No (matched cases and controls)	No	No (multivariable analysis)	No	
Stuart, 2003	No (matched cases and controls)	No	No (multivariable analysis)	No	
Valderrama, 2009	No (matched cases and controls)	No	No (multivariable analysis)	No	

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	0	
Imprecision	-1	Low number of events, lack of data or large variability in results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low[D]**	

Conclusion	**Swimming** It was shown that the following risk factors resulted in a statistically significant increased risk of *Cryptosporidium/Giardia* infection: exposure to any recreational water, recreational fresh water contact, and swallowed water while swimming (Valderrama 2009, Stuart 2003). A statistically significant increased risk of *Campylobacter* infection in case of using a public swimming pool compared to not doing this could not be demonstrated (Schorr 1994). Evidence is of very low quality and results cannot be considered precise due to limited sample size, lack of data and large variability of results. **Drinking tap water** There is conflicting evidence concerning drinking tap water. It was shown that drinking only tap water vs drinking only bottled or filtered water resulted in a statistically significant decreased risk of *Salmonella infantis* infection (Bassal 2013). On the other hand, each additional glass of tap water consumed per day resulted in an increased risk of giardiasis (Stuart 2003). It must be noted that evidence concerning tap water is very context/region-dependent. A statistically significant increased risk of travelers' diarrhoea in case of consuming tap water abroad compared to not doing this could not be demonstrated (Pitzurra 2010). Evidence is of very low quality and results cannot be considered precise due to limited sample size, lack of data and large variability of results.
Reference(s)	**Articles** Bassal R, Reisfeld A, Nissan I, Agmon V, Taran D, Schemberg B, Cohen D, Shohat T. *Risk factors for sporadic infection with Salmonella Infantis: A matched case-control study*. ***Epidemiol Infect*** 2013, **142(**4): 820-5 Pitzurra R, Steffen R, Tschopp A, Mutsch M. *Diarrhoea in a large prospective cohort of European travellers to resource-limited destinations*. BMC Infect Dis 2010, 10:231 Schorr D, Schmid H, Rieder HL, Baumgartner A, Vorkauf H, Burnens A. *Risk factors for Campylobacter enteritis in Switzerland*. Zentralbl Hyg Umweltmed 1994, 196(4):327-37 Stuart JM, Orr HJ, Warburton FG, Jeyakanth S, Pugh C, Morris I, Sarangi J, Nichols G. *Risk factors for sporadic giardiasis: a case-control study in southwestern England*. Emerg Infect Dis 2003, 9(2):229-33 Valderrama AL, Hlavsa MC, Cronquist A, Cosgrove S, Johnston SP, Roberts JM, Stock ML, Xiao L, Xavier K, Beach MJ. *Multiple risk factors associated with a large statewide increase in cryptosporidiosis*. Epidemiol Infect 2009, 137(12):1781-8

Diarrhoea & dehydration – Food (Risk factor)

Question (PICO)	In humans (P), is eating certain food (I) a risk factor for diarrhoea or dehydration (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search term: 1. [mh "Diarrhea"] OR [mh "Dehydration"] OR diarrhoea:ti,ab OR diarrhoea:ti,ab OR diarrhea:ti,ab 2. [mh "Risk factors"] OR (risk NEXT factor*):ti,ab 3. 1-2 AND

	MEDLINE (via PubMed interface) for guidelines and systematic reviews using the following search strategy: 1. "Diarrhea"[Mesh] OR "Dehydration"[Mesh] OR diarrhea[TIAB] OR diarrhoea[TIAB] OR dehydration[TIAB] 2. "Food handling"[Mesh] OR "Food Contamination"[Mesh] OR "Hygiene"[Mesh] OR "Drinking"[Mesh] OR "Eating"[Mesh] OR "Food"[Mesh] OR kitchen[TIAB] OR hygiene[TIAB] OR drinking[TIAB] OR eating[TIAB] OR bottle[TIAB] OR spicy[TIAB] OR spices[TIAB] OR coffee[TIAB] OR raw[TIAB] 3. "Risk factors"[Mesh] OR risk factor*[TIAB] 4. "Epidemiologic Studies"[Mesh] OR "case-control"[TIAB] OR ((case[TIAB] OR cases[TIAB]) AND (control[TIAB] OR controls[TIAB])) OR "cohort study"[TIAB] OR "cohort analysis"[TIAB] OR "follow-up study"[TIAB] OR "observational study"[TIAB] OR "longitudinal"[TIAB] OR "retrospective"[TIAB] 5. 1-4 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'diarrhea'/exp OR 'dehydration'/exp OR diarrhea:ab,ti OR diarrhoea:ab,ti OR dehydration:ab,ti 2. 'food handling'/exp OR 'food contamination'/exp OR 'hygiene'/exp OR 'drinking'/exp OR 'eating'/exp OR 'food'/exp OR kitchen:ab,ti OR hygiene:ab,ti OR drinking:ab,ti OR eating:ab,ti OR bottle:ab,ti OR spicy:ab,ti OR spices:ab,ti OR coffee:ab,ti OR raw:ab,ti 3. 'risk factor'/exp OR (risk NEXT/1 factor*):ab,ti 4. 'cohort analysis'/exp OR 'case-control':ab:ti OR ((case:ab:ti OR cases:ab:ti) AND (control:ab:ti OR controls:ab:ti)) OR 'cohort study':ab:ti OR 'cohort analysis':ab:ti OR 'follow-up study':ab:ti OR 'observational study':ab:ti OR 'longitudinal':ab:ti OR 'retrospective':ab:ti 5. 1-4 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	24 August 2015
Inclusion/Exclusion criteria	**Population**: Include: people in developed countries (according to definition of Worldbank and statistics of the International Statistical Institute); travellers from developed countries (also travelling to developing countries); cases have diarrhoea from various origin (infection with *Campylobacter*, *Cryptosporidium*, *Escherichia coli* 0157:H7, *Salmonella*, *Giardia* or origin of diarrhoea not mentioned; remark: since a *Giardia* infection can occur asymptomatic, only studies were included where presence of diarrhoea was explicitly mentioned), but have no other illnesses; controls are healthy; Exclude: neonates; inhabitants of a region where an epidemic or outbreaks occurs; people residing in refugee camps or a disaster setting; victims of nosocomial infections **Intervention**: Include: modifiable, proximal risk factor with a potential immediate implication for practice that results in primary prevention at the household or community level. Risk factors related to healthy persons; risk factors that are relevant for European inhabitants or travellers; Exclude: risk factors that do not precede the outcome; risk factors that are common sense; risk factors concerning water purification, hand washing and latrine use (since these are covered in other PICO's); risk factors concerning breastfeeding or the use of concentrated infant formula (not proximal/not always modifiable); travelling as such as a risk factor was excluded (not modifiable), however specific risk factors relevant during travelling were included **Outcome**: Include: (risk of) diarrhoea, risk of *Salmonella*/*Campylobacter*/*Cryptosporidium*/*E. coli* 0157:H7 infection; dehydration; only data from multivariate analysis were extracted, i.e. data that were adjusted for confounding variables; Exclude: (risk of) hospital admission, chronic diarrhoea, data from univariate analysis (unadjusted)

	Design: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An observational study: inclusion in case of one of the following study types: cohort and case-control study (taking into account confounding variables at the analysis phase), controlled before and after study or controlled interrupted time series, and the data are available. Exclude: observational studies not taking into account confounding variables at the analysis phase, conference abstracts, case series, cross-sectional studies (studies collecting information concerning type of car and injury in health insurance companies), animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline)

Characteristics of included studies

Author, year, Country	Study design	Population	Risk factor	Remarks
Bassal, 2013, Israel	Observational: case-control study	Cases (n=263): culture-confirmed symptomatic patients diagnosed as having *Salmonella infantis* infection; 77 children ≤ 1 year; mean age of cases > 1 year: 22.8 years Controls (n=263): healthy controls through the Israeli Population Register, matched by gender, age and neighbourhood	Multiple risk factors: breastfeeding and formula use (for infants), contact with animals, and exposure to various food items (including eggs, poultry and meat, dairy products, fruits and vegetables), food handling and water consumption	A comprehensive structured questionnaire was administered by telephone to all the cases and controls. A multivariable analysis was performed.
Delarocque-Astagneau, 1998, France	Observational: case-control study	Cases (n=105): children ≤ 5 years old residing in France with fever (temperature > 38°C) or diarrhoea (≥ 3 loose stools per day for more than 1 day) in association with the isolation of *Salmonella enteritidis* from stool or blood Controls (n=105): For each case, one control of the same age group and the same city or county, who had had no gastro-intestinal symptoms during the month prior to onset of illness in the case	Multiple risk factors: consumption, purchase, storage and preparation habits of eggs and egg products, poultry meat and beef meat, contact with persons who had diarrhoea, day-care or nursery attendance	The investigator interviewed parents of cases and controls by telephone, using a pre-tested standardized questionnaire. A conditional logistic regression was performed, however only data on the statistically significant results were provided.
Delarocque-Astagneau, 2000, France	Observational: case-control study	Cases (n=101): children < 14 years old residing in metropolitan France with fever (temperature >	Multiple risk factors: consumption, purchase, storage, and preparation habits for various food	An interview by telephone, using a pretested,

		38°C) or diarrhoea (≥ 3 loose stools per day for > 1 day) in association with the isolation of *Salmonella typhimurium* from stool or blood Controls (n=101): Control subjects were matched to case patients according to age and place of residence	items such as eggs and egg products, poultry, beef (e.g., for ground beef, the extent to which it was cooked and consumed in dishes such as bolognaise and shepherd's pie), and shellfish ; contact with persons who had diarrhoea; attendance at a day-care facility or nursery	standardized questionnaire, was performed. A multivariate analysis was performed, however only data on the statistically significant results were provided.
Doré, 2004, Canada	Observational: case-control study	Cases (n=396): individuals with diarrhoeal illness who had *Salmonella typhimurium* non-DT104 (n=258) (mean age 13 years) and DT104 (n=138) (mean age 19 years) isolated from stool samples Controls (n=396): randomly selected from provincial Ministry of Health registered persons databases, matched on age and province of residence	Multiple risk factors: health history including previous medication use; recent travel history; animal contact; consumption of raw fruits and vegetables, unpasteurized dairy products, raw or undercooked eggs and meats ; meals eaten outside the home; drinking water source; food hygiene practices and day-care attendance	Cases and controls were interviewed by telephone using a pre-tested, standardized questionnaire. A multivariable analysis using conditional logistic regression was performed.
Fullerton, 2007, USA	Observational: case-control study	Cases (n=123): Infants 0–6 months of age with *Campylobacter* infection Controls (n=928): were randomly selected from birth registries in each state, matched to cases by age and state of residence	Multiple risk factors: environmental exposures (household exposures, child care settings, animals, petting zoos and farms and international travel) and food exposures (breast-feeding, formula, water and solid food)	A standard questionnaire was administered by telephone to parents/ guardians of cases and controls. Multivariable unconditional logistic regression models were applied.
Holton, 1999, Canada	Observational: case-control study	Cases (n=100): persons with gastrointestinal symptoms and a positive stool culture for *E. coli* 0157:H7 (median age: 17.5 years) Controls (n=200): Two neighbourhood residents matched to each case by age	Multiple risk factors: contact with persons suffering from diarrheal illness; consumption, handling and preparation of ground beef and ground beef patties; consumption of other beef cuts and ground meats; consumption of other types of foods; and	Cases and controls were interviewed face-to-face to obtain information on potential risk factors for infection and health outcomes.

		and sex were recruited as controls according to a standardized protocol Infants under one year of age were excluded.	presence in settings where ground beef was eaten	A multivariable analysis was performed.
Jones, 2006, USA	Observational: case-control study	Cases (n=442): infants < 1 year with from whom any serotype of *Salmonella* other than Typhi was isolated from a clinical specimen Controls (n=928): identified through birth registries or published birth announcements, and matched by age	Multiple risk factors: water source, formula types, various foods and manner of preparation, previous antibiotic use, and animal exposures	An extensive questionnaire was administered by telephone to the parents or guardians of the subjects and controls. A multivariable regression analysis was performed.
Kassenborg, 2004, USA	Observational: case-control study	Cases (n=196): patients with non–outbreak-related diarrheal illness who had O157 isolated from their stool samples (*E. coli* O157:H7) (median age: 12 years) Controls (n=372): healthy persons matched by age and telephone number exchange	Multiple risk factors: antibiotic and antacid use, any immune compromising conditions or chronic illnesses that existed in the 4 weeks before the case patient's onset of illness, travel, child day care, exposure to farms and cows, meat handling practices, sources of drinking water and ground beef, and consumption of fruits, vegetables, and meats during the 5-day period before the case patient's date of disease onset	Case patients were interviewed within 21 days of their stool sample collection date, and controls were interviewed within 7 days after the patient's interview. A multivariate analysis was performed.
Kist, 2000, Germany	Observational: case-control study	Cases (n=965): diarrhoeic and/or febrile illness and isolation of *Salmonella enteritidis* (n=790) or non-enteritidis Salmonella (n=175) in their stool Controls (n=256): healthy individuals, called by phone in the Freiburg study area (people reporting symptoms compatible with enteric infection were excluded); matching by age group and sex was done	Multiple risk factors: place of residence, foreign travel during 2 weeks before onset of symptoms, preceding (2 weeks) fever or diarrhoea in contact persons, prior (1 month) consumption of antacids or antimicrobials, consumption of various food during 48 h before onset of symptoms, and contact with domestic and farm animals and pets	Cases were interviewed by their physician; controls were interviewed via telephone. A multivariable logistic regression analysis was performed.

Pitzurra, 2010, Switzerland	Observational: cohort study	2800 travellers to a resource-limited country for the duration of 1 to 8 weeks. 962 travellers had travellers' diarrhoea, 1838 had not	Multiple risk factors: previous travel to the tropics, demographic data, body mass index, chronic diseases, confirmed allergies, and pretravel diarrhoea characteristics, adverse life events in the preceding 12 months, self-reported stress, smoking habits and alcohol consumption, perceived susceptibility to diarrhoea, attitudes towards diarrhoea (catering, adherence to 'cook it, boil it, peel it or forget it', tap water consumption)	Upon signing an informed consent, the participants received two questionnaires. Q1 was collected immediately upon completion, while Q2 was to be returned in the first week after their return reminded either by mail or email; Q2 was similar to a diary. A multiple logistic regression model was used.
Robertson, 2002, Australia	Observational: case-control study	Cases (n=134): people having *Cryptosporidium* oocysts detected in a faecal specimen by an accredited pathology laboratory, the onset of any diarrhoea or vomiting within 8 weeks before the administration of questionnaire, residence in a household with a fixed telephone connection and the ability to speak English (median age: 11 years) Controls (n=536): people not having diarrhoea or vomiting in the 2 weeks before the onset of the matching case's illness, residence in a household with a fixed telephone connection and the ability to speak English	Multiple risk factors: education level, employment, the consumption of tap water, the consumption of particular food groups, recreational water activities, the presence of immunological impairment, the consumption of regular medication, contact with persons who may pose a risk of cryptosporidiosis, animal contact, rural or overseas travel and exposure to child-care or breast feeding.	A computer assisted telephone questionnaire was used. A stratified Cox proportional hazard regression analysis was performed. Data were collected in Melbourne and Adelaide. Only data that were consistently significant (or not) at both sites were extracted. Only Melbourne data were extracted.
Schorr, 1994, Switzerland	Observational: case-control study	Cases (n=167): people ≥ 15 years and < 65 years with gastrointestinal symptoms (mostly diarrhoea) and whose stool specimen was	Multiple risk factors: information on food preferences, and contained questions on a number of specific food items consumed in the	Risk factors were assessed through questionnaires.

		submitted for culture to one of the participating laboratories yielded *Campylobacter* Controls (n=282): people who had no diarrheal illness within two weeks before completing the control questionnaire, matched for sex	five days preceding onset of symptoms, and further factors considered to be potential risk factors for the disease under study (travel abroad, water consumption, pet animals, predisposing factors like use of antacids and antibiotics or serious medical conditions)	A multivariate analysis was performed.
Stuart, 2003, UK	Observational: case-control study	Cases (n=232): residents of the study area with a history of diarrhoea and *Giardia* cysts in their stool specimen seen by light microscopy (cases were most frequent in the 30- to 39-year age group) Controls (n=574): persons registered at the same general practice as patients, of the same gender, and in the same broad age band (0–5 years, 6–15 years, >16 years)	Multiple risk factors: recent illness, travel, water contact, water and food consumption (food history focusing on dairy produce, salads, fruit), and contact with animals, farms, and day nurseries	Information from cases and controls was collected through interviews. A multivariable conditional logistic regression analysis was performed.
Valderrama, 2009, USA	Observational: case-control study	Cases (n=45): Colorado resident who had a positive *Cryptosporidium* laboratory stool test (median age: 19 years) Controls (n=89):a Colorado resident who had experienced no gastrointestinal symptoms, matched by age and geographic area	Multiple risk factors: food and water consumption, recreational water exposure, child care and household exposures, farm and animal contact, person-to-person contact, and travel history during the exposure period as well as basic demographics	A standardized questionnaire was developed and administered by telephone. Case-patients and corresponding matched controls were asked about possible exposures during the 2 weeks prior to the case-patient's onset of symptoms. A multivariable analysis was performed.

Synthesis of findings

Outcome	Risk factor	Effect Size	#studies, # participants	Reference
Meat/hamburger				
Risk of *E. coli* 0157:H7 infection	Ate pink ground beef in seven days before illness vs not	Statistically significant: OR: 6.16, 95%CI [1.24;59.73] (p=0.011) £†	1, 100 vs 200	Holton, 1999

		with harm for eating pink ground beef		
	Ate pink ground beef patties in seven days before illness vs not	Statistically significant: OR: 19.56, 95%CI [2.98;828.73] (p=0.00004) £† *with harm for eating pink ground beef patties*		
	Attendance at a picnic or special event where ground beef was served in seven days before illness vs not	Not statistically significant: OR: 1.64, 95%CI [0.08;3.33] ¥ (p=0.0946) £†		
	Ate a hamburger cooked less than usual in seven days before illness vs not	Statistically significant: OR: 20.12, 95%CI [2.92;868.01] (p=0.0001) £† *with harm for eating a hamburger cooked less than usual*		
	Ate at table-service restaurant vs not	Statistically significant: 91/193 vs 127/357 § OR: 1.7, 95%CI [1.0;2.9] (p=0.04) *with harm for eating at a table-service restaurant*	1, 193 vs 357	Kassenborg, 2004
	Ate pink hamburger at home vs not	Statistically significant: 16/170 vs 15/338 § OR: 5.0, 95%CI [1.7;15] (p=0.004) *with harm for eating a pink hamburger at home*	1, 170 vs 338	
	Ate pink hamburger away from home vs not	Statistically significant: 13/153 vs 5/316 § OR: 5.0, 95%CI [1.3;20] (p=0.02) *with harm for eating a pink hamburger away from home*	1, 153 vs 316	
Risk of *Salmonella typhimurium* infection	Consumption of raw or undercooked ground beef vs not	Statistically significant: OR: 3.8, 95% CI [1.7;8.4] (p<0.05) £† *with harm for consumption of raw or undercooked ground beef*	1, 101 vs 101	Delarocque-Astagneau, 2000
Risk of *Salmonella* infection	Consumption of raw or undercooked meat vs not	Not statistically significant: OR: 1.7 (p=0.4) ££†	1, 965 vs 790	Kist, 2000
Risk of *Campylobacter* infection	Consumption of ground raw beef (tartar) vs not	Not statistically significant: OR: 0.3, 95%CI [0.1;1.5] ¥ (p>0.05) £†	1, 167 vs 282	Schorr, 1994
	Consumption of hamburger vs not	Not statistically significant: OR: 0.6, 95%CI [0.3;1.1] ¥ (p>0.05) £†		
	Consumption of roast beef vs not	Not statistically significant: OR: 0.6, 95%CI [0.2;1.4] ¥ (p>0.05) £†		
Risk of *Salmonella typhimurium* infection	Consumption of foods containing thoroughly cooked ground beef vs not	Statistically significant: OR: 0.4, 95% CI [0.2;0.8] (p<0.05) £† *with benefit for consumption of foods containing thoroughly cooked ground beef*	1, 101 vs 101	Delarocque-Astagneau, 2000

Risk of *Campylobacter* infection	Preparing hamburger in the home vs not	Statistically significant: 57/113 vs 502/907 OR: 0.6, 95%CI [0.3;0.9] (p<0.05) *with benefit for preparing a hamburger in the home*	1, 123 vs 928	Fullerton, 2007
Risk of *E. coli* 0157:H7 infection	Ground beef prepared in the home in seven days before illness vs not	Statistically significant: OR: 0.54, 95%CI [0.31;0.92] (p=0.011) £† *with benefit for ground beef prepared in the home*	1, 100 vs 200	Holton, 1999
Risk of non-typhimurium *Salmonella* infection	Any meat or poultry prepared in home vs not	Statistically significant: OR: 0.5, 95%CI [0.4;0.7] (p<0.05) £† *with benefit for any meat or poultry prepared in home*	1, 442 vs 928	Jones, 2006
Chicken				
Risk of *Salmonella* infection	Consumption of poultry vs not	Not statistically significant: OR: 1.1 (p=0.6) ££†	1, 965 vs 790	Kist, 2000
Risk of *Salmonella infantis*	Thawing chicken in water vs not	Not statistically significant: OR: 2.55, 95%CI [0.94;6.91] ¥ (p=0.07) £†	1, 263 vs 263	Bassal, 2013
Risk of *Campylobacter* infection	Consumption of poultry vs not	Not statistically significant: OR: 1.8, 95%CI [1.0;3.4] (p>0.05) £†	1, 167 vs 282	Schorr, 1994
	Consumption of poultry liver vs not	Statistically significant: OR: 5.7, 95%CI [1.4;22.8] (p<0.05) £† *with harm for consumption of poultry liver*		
	Consumption of poultry terrine vs not	Not statistically significant: OR: 0.4, 95%CI [0.1;2.7] ¥ (p>0.05) £†		
	Preparation of food from frozen poultry vs not	Not statistically significant: OR: 0.5, 95%CI [0.2;1.6] ¥ (p>0.05) £†		
	Preparation of poultry personally vs not	Not statistically significant: OR: 2.0, 95%CI [0.9;4.7] ¥ (p>0.05) £†		
	Preparing chicken in the home vs not	Not statistically significant: 83/115 vs 629/910 OR: 1.2, 95%CI [0.7;2.0] ¥ (p>0.05)	1, 123 vs 928	Fullerton, 2007
Carrots				
Risk of *Cryptosporidium* infection	Uncooked carrots vs not	Statistically significant: OR: 0.6, 95%CI [0.4;0.9] (p<0.05) £† *with benefit for uncooked carrots*	1, 134 vs 536	Robertson, 2002
Risk of *Salmonella infantis* infection	Consumption of carrots vs not	Statistically significant: OR: 0.46, 95%CI [0.26;0.83] (p<0.01) £† *with benefit for consumption of carrots*	1, 263 vs 263	Bassal, 2013
Eggs				
Risk of *Salmonella infantis* infection	Consumption of eggs vs not	Not statistically significant: OR: 1.87, 95%CI [1.00;3.49] ¥ (p=0.05) £†	1, 263 vs 263	Bassal, 2013

Risk of non-typhimurium *Salmonella* infection	Consumed partially cooked egg vs not	Not statistically significant: OR: 2.7, 95%CI [0.9;7.6] ¥ (p>0.05) £†	1, 442 vs 928	Jones, 2006
Risk of *Salmonella enteritidis* infection	Storage of eggs > 2 weeks vs not	Statistically significant: OR: 3.6, 95%CI [1.3;9.8] (p<0.05) £† *with harm for storage of eggs > 2 weeks*	1, 105 vs 105	Delarocque-Astagneau, 1998
	Consumption of raw or undercooked eggs vs not	Not statistically significant: OR: 2.0, 95%CI [1.0;3.8] ¥ (p>0.05) £†		
Risk of *Salmonella* infection	Consumption of raw eggs vs not	Statistically significant: OR: 30.3 (p=0.001) ££† *with harm for consumption of raw eggs*	1, 965 vs 790	Kist, 2000
	Consumption of raw or undercooked eggs vs not	Statistically significant: OR: 1.9 (p=0.003) ££† *with harm for consumption of raw or undercooked eggs*		
Cream/milk/cheese				
Risk of *Campylobacter* infection	Consumption of unpast cream vs not	Not statistically significant: OR: 0.7, 95%CI [0.3;2.0] ¥ (p>0.05) £†	1, 167 vs 282	Schorr, 1994
	Consumption of raw milk vs not	Not statistically significant: OR: 0.9, 95%CI [0.4;2.1] ¥ (p>0.05) £†		
	Consumption of curd/cottage cheese vs not	Statistically significant: OR: 0.5, 95%CI [0.3;0.9] (p<0.05) £† *with harm for consumption of curd/cottage cheese*		
Salad				
Risk of *Salmonella* Typhimurium non-DT104 infection	Ate green salad vs not	Statistically significant: OR: 0.4, 95%CI [0.2;0.7] (p=0.001) £† *with benefit for eating green salad*	1, 194 vs 194	Doré, 2004
Risk of *Salmonella* Typhimurium DT104	Ate green salad vs not	Not statistically significant: OR: 0.5, 95%CI [0.3;1.0] ¥ (p=0.05) £†	1, 123 vs 123	
Risk of giardiasis	Ate lettuce vs not	Statistically significant: OR: 2.2, 95% CI [1.1;4.3] (p=0.01) £† *with harm for eating lettuce*	1, 232 vs 574	Stuart, 2003
Other risk factors				
Risk of *Salmonella* Typhimurium non-DT104 infection	Consumed fresh fruit juice vs not	Statistically significant: OR:0.3, 95%CI [0.2;0.7] (p=0.01) £† *with benefit for consuming fresh fruit juice*	1, 194 vs 194	Doré, 2004
Risk of giardiasis	Ate ice cream vs not	Statistically significant: OR: 0.4, 95% CI [0.2;0.7] (p=0.002) £† *with benefit for eating ice cream*	1, 232 vs 574	Stuart, 2003
Risk of travellers' diarrhoea	Adherence to "Cook it, boil it, peel it, or forget it" vs not	Not statistically significant: OR: 1.00, 95%CI [0.79;1.27] ¥ (p>0.05) £†	1, 2565 (no information available about	Pitzurra, 2010

			number of cases and controls)	
Risk of *E. coli* 0157:H7 infection	Diet variability vs not	Statistically significant: 116/192 vs 300/366 OR: 0.4, 95%CI [0.2;0.7] (p=0.007) *with benefit for diet variability*	1, 192 vs 366	Kassenborg, 2004
Risk of *Cryptosporidium* infection	Consumption of produce from farm/farm stand vs not	Statistically significant: 8/45 vs 35/89 § OR: 0.2, 95%CI [0.1;0.9] (p<0.05) *with benefit for consumption of produce from farm/farm stand*	1, 45 vs 89	Valderrama, 2009
Risk of *Campylobacter* infection	Consumption of raw oysters vs not	Not statistically significant: OR: 0.4, 95%CI [0.1;2.7] ¥ (p>0.05) £†	1, 167 vs 282	Schorr, 1994

£ No raw data available
££ No raw data and CI available
§ Imprecision (low number of events)
† Imprecision (lack of data)
¥ Imprecision (large variability of results)

Quality of evidence

Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations
Bassal, 2013	No (matched cases and controls)	No	No (multivariable analysis)	No	
Delarocque-Astagneau, 1998	No (matched cases and controls)	No	No (multivariable analysis)	No	
Delarocque-Astagneau, 2000	No (matched cases and controls)	No	No (multivariable analysis)	No	
Doré, 2004	No (matched cases and controls)	No	No (multivariable analysis)	No	
Fullerton, 2007	No (matched cases and controls)	No	No (multivariable analysis)	No	
Holton, 1999	No (matched cases and controls)	No	No (multivariable analysis)	No	
Jones, 2006	No (matched cases and controls)	No	No (multivariable analysis)	No	
Kassenborg, 2004	No (matched cases and controls)	No	No (multivariable analysis)	No	
Kist, 2000	No (matched cases and controls)	Yes, possible differences in how risk factors were assessed in cases and controls: cases were interviewed by their	No (multivariable analysis)	No	

		physician; controls were interviewed via telephone			
Pitzurra, 2010	No (comparable demographics)	No	No (multivariable analysis)	No	
Robertson, 2002	No (matched cases and controls)	No	No (multivariable analysis)	No	
Schorr, 1994	No (matched cases and controls)	No	No (multivariable analysis)	No	
Stuart, 2003	No (matched cases and controls)	No	No (multivariable analysis)	No	
Valderrama, 2009	No (matched cases and controls)	No	No (multivariable analysis)	No	

	Initial grading Low [C]	Downgrading due to
Limitations of study design	0	
Imprecision	-1	Low number of events, lack of data or large variability in results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low[D]**	

Conclusion	**Meat/hamburger** It was shown that the following risk factors resulted in a statistically significant increased risk of *E. coli* 0157:H7 or Salmonella infection: eating pink ground beef, eating pink ground beef patties, eating a hamburger cooked less than usual, eating at table-service restaurant, eating pink hamburger at home, eating pink hamburger away from home and consumption of raw or undercooked ground beef (Holton 1999, Kassenborg 2004, Delarocque-Astagneau 2000). It was shown that the following risk factors resulted in a statistically significant decreased risk of *Salmonella*/*Campylobacter*/*E. coli* 0157:H7 infection: Consumption of foods containing thoroughly cooked ground beef, Preparing hamburger/ground beef/poultry/any meat in the home (Delarocque-Astagneau 2000, Fullerton 2007, Holton 1999, Jones 2006). Evidence is of very low quality and results cannot be considered precise due to limited sample size, lack of data and large variability of results. **Chicken** It was shown that the following risk factor resulted in a statistically significant increased risk of *Campylobacter* infection: consumption of poultry liver (Schorr 1994). A statistically significant increased risk of *Salmonella*/*Campylobacter* infection in case of consumption of poultry, thawing chicken in water, consumption of poultry terrine or preparation of food from frozen poultry could not be demonstrated (Kist 2000, Bassal 2013, Schorr 1994). A statistically significant decreased risk of *Campylobacter* infection in case of preparation of poultry personally or preparing chicken in the home could not be demonstrated (Schorr 1994, Fullerton 2007). Evidence is of very low quality and results cannot be considered precise due to limited sample size, lack of data and large variability of results. **Carrots** It was shown that the following risk factors resulted in a statistically significant decreased risk of *Cryptosporidium*/*Salmonella* infection: eating uncooked carrots and consumption of carrots (Robertson 2002, Bassal 2013). Evidence is of very low quality and results cannot be considered precise due to limited sample size, lack of data and large variability of results. **Eggs** It was shown that the following risk factors resulted in a statistically significant increased risk of *Salmonella* infection: storage of eggs > 2 weeks and consumption of raw or undercooked eggs (Delarocque-Astagneau 1998, Kist 2000). A statistically significant increased risk of *Salmonella* infection in case of consumption of raw or undercooked eggs could not be demonstrated in two smaller studies (Delarocque-Astagneau 1998, Jones 2006). In addition, the consumption of eggs (cooked or raw) could not be demonstrated as a risk factor (Bassal 2013). Evidence is of very low quality and results cannot be considered precise due to limited sample size, lack of data and large variability of results. **Cream/milk/cheese** It was shown that the following risk factor resulted in a statistically significant increased risk of *Campylobacter* infection: consumption of curd/cottage cheese (Schorr 1994). A statistically significant increased risk of *Salmonella* infection in case of consumption of unpast cream and consumption of raw milk could not be demonstrated (Schorr 1994). Evidence is of very low quality and results cannot be considered precise due to limited sample size, lack of data and large variability of results. **Salad** There is conflicting evidence concerning eating salad. It was shown that eating lettuce resulted in a statistically significant increased risk of giardiasis (Stuart 2003). On the other hand it was shown that eating green salad resulted in a statistically significant decreased

	risk of *Salmonella* Typhimurium non-DT104 infection (Doré 2004). A statistically significant difference in the risk of *Salmonella* Typhimurium DT104 infection in case of eating green salad could not be demonstrated (Doré 2004). The way the salad is treated (insecticide? washed?) is unknown and could be a confounding factor, explaining the inconsistency between studies. Evidence is of very low quality and results cannot be considered precise due to limited sample size, lack of data and large variability of results. **Other risk factors** It was shown that the following risk factors resulted in a statistically significant decreased risk of *Salmonella/Giardia/Cryptosporidium/E. coli* 0157:H7 infection: consumption of fresh fruit juice, eating ice cream, diet variability and consumption of produce from farm/farm stand (Doré 2004, Stuart 2003, Kassenborg 2004, Valderrama 2009). Some explanation concerning these protecting factors are provided by the study authors: (1) the negative association between illness and eating ice cream is unlikely to represent a true protective effect (Stuart 2003), (2) it is possible that the consumption of fresh fruit juice may be protective, through as yet speculative mechanisms, or they may be indicators of nutritional status and possibly be related to better health in general (Doré 2004), (3) an explanation for the protective effect of consumption of produce from a farm may be that continued consumption of contaminated produce may provide protection against overt cryptosporidiosis by keeping antibody levels raised since antibody to the parasite appears to protect from subsequent illness rather than re-infection (Valderrama 2009). A statistically significant increased risk of *Campylobacter* infection in case of consumption of raw oysters could not be demonstrated (Schorr 1994). A statistically significant increased risk of travellers' diarrhoea in case of adherence to "Cook it, boil it, peel it, or forget it" could not be demonstrated (Pitzurra 2010). Evidence is of very low quality and results cannot be considered precise due to limited sample size, lack of data and large variability of results.
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Diarrhoea & dehydration – Kitchen hygiene (Risk factor)

Question (PICO)	In humans (P), is kitchen hygiene (I) a risk factor/protective factor for diarrhoea or dehydration (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search term: 1. [mh "Diarrhea"] OR [mh "Dehydration"] OR diarrhoea:ti,ab OR diarrhoea:ti,ab OR diarrhea:ti,ab 2. [mh "Risk factors"] OR (risk NEXT factor*):ti,ab 3. 1-2 AND **MEDLINE** (via PubMed interface) for guidelines and systematic reviews using the following search strategy: 1. "Diarrhea"[Mesh] OR "Dehydration"[Mesh] OR diarrhea[TIAB] OR diarrhoea[TIAB] OR dehydration[TIAB] 2. "Food handling"[Mesh] OR "Food Contamination"[Mesh] OR "Hygiene"[Mesh] OR "Drinking"[Mesh] OR "Eating"[Mesh] OR "Food"[Mesh] OR kitchen[TIAB] OR hygiene[TIAB] OR drinking[TIAB] OR eating[TIAB] OR bottle[TIAB] OR spicy[TIAB] OR spices[TIAB] OR coffee[TIAB] OR raw[TIAB] 3. "Risk factors"[Mesh] OR risk factor*[TIAB] 4. "Epidemiologic Studies"[Mesh] OR "case-control"[TIAB] OR ((case[TIAB] OR cases[TIAB]) AND (control[TIAB] OR controls[TIAB])) OR "cohort study"[TIAB] OR "cohort analysis"[TIAB] OR "follow-up study"[TIAB] OR "observational study"[TIAB] OR "longitudinal"[TIAB] OR "retrospective"[TIAB] 5. 1-4 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'diarrhea'/exp OR 'dehydration'/exp OR diarrhea:ab,ti OR diarrhoea:ab,ti OR dehydration:ab,ti 2. 'food handling'/exp OR 'food contamination'/exp OR 'hygiene'/exp OR 'drinking'/exp OR 'eating'/exp OR 'food'/exp OR kitchen:ab,ti OR hygiene:ab,ti OR drinking:ab,ti OR eating:ab,ti OR bottle:ab,ti OR spicy:ab,ti OR spices:ab,ti OR coffee:ab,ti OR raw:ab,ti 3. 'risk factor'/exp OR (risk NEXT/1 factor*):ab,ti 4. 'cohort analysis'/exp OR 'case-control':ab:ti OR ((case:ab:ti OR cases:ab:ti) AND (control:ab:ti OR controls:ab:ti)) OR 'cohort study':ab:ti OR 'cohort analysis':ab:ti

	OR 'follow-up study':ab:ti OR 'observational study':ab:ti OR 'longitudinal':ab:ti OR 'retrospective':ab:ti 5. 1-4 AND A systematic review of 2008 was selected. No more recent individual studies were identified.
Search date	24 August 2015
Inclusion/Exclusion criteria	**Population**: Include: people in developed countries (according to definition of Worldbank and statistics of the International Statistical Institute); travellers from developed countries (also travelling to developing countries); cases have diarrhoea from various origin (infection with *Campylobacter*, *Cryptosporidium*, *Escherichia coli* 0157:H7, *Salmonella*, *Giardia* or origin of diarrhoea not mentioned; remark: since a *Giardia* infection can occur asymptomatic, only studies were included where presence of diarrhoea was explicitly mentioned), but have no other illnesses; controls are healthy; Exclude: neonates; inhabitants of a region where an epidemic or outbreaks occurs; people residing in refugee camps or a disaster setting; victims of nosocomial infections **Intervention**: Include: modifiable, proximal risk factor with a potential immediate implication for practice that results in primary prevention at the household or community level. Risk factors related to healthy persons; risk factors that are relevant for European inhabitants or travellers; Exclude: risk factors that do not precede the outcome; risk factors that are common sense; risk factors concerning water purification, hand washing and latrine use (since these are covered in other PICO's); risk factors concerning breastfeeding or the use of concentrated infant formula (not proximal/not always modifiable); travelling as such as a risk factor was excluded (not modifiable), however specific risk factors relevant during travelling were included **Outcome**: Include: (risk of) diarrhoea, risk of *Salmonella*/*Campylobacter*/*Cryptosporidium*/*E. coli* 0157:H7 infection; dehydration; only data from multivariate analysis were extracted, i.e. data that were adjusted for confounding variables; Exclude: (risk of) hospital admission, chronic diarrhoea, data from univariate analysis (unadjusted) **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An observational study: inclusion in case of one of the following study types: cohort and case-control study (taking into account confounding variables at the analysis phase), controlled before and after study or controlled interrupted time series, and the data are available. Exclude: observational studies not taking into account confounding variables at the analysis phase, conference abstracts, case series, cross-sectional studies (studies collecting information concerning type of car and injury in health insurance companies), animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline)

Characteristics of included studies

Author, year, Country	Study design	Population	Risk factor	Remarks
Stenberg, 2008, UK	Systematic review	14 studies, including 11 case-control studies, 2 cross-sectional surveys, and 1 RCT Those studies whose participants were households, children or adults from developed countries were included.	Multiple risk factors concerning kitchen hygiene (concerning cleanliness, preparation and storage of food) [data from the cross-sectional surveys and RCT (comparison not relevant) were not	Complete data are available in "Additional file 1" of the systematic review. Data from the following studies were extracted: Kohl 2002, Neimann 2003, Parry 2002, Mead

		The outcomes included were either self- reported diarrhoea with no associated pathogen identified or cases of diarrhoea with a known enteric pathogen identified.	extracted; data from studies that took not into account confounding variables at the analysis stage were not extracted]	1997, and the UK IID study (data reported in Stenberg 2008). The study of Mitatakakis (2004) was not included since it was not clear if the provided data were the result of a multivariable analysis.

Synthesis of findings

Outcome	Risk factor	Effect Size	#studies, # participants	Reference
Preparation of food				
Risk of diarrhoea	Frequently defrosting chicken in microwave vs not	Statistically significant: OR: 2.5, 95%CI [1.5;4.0] (p<0.05) £† *With harm for frequently defrosting chicken in microwave*	1, 687 vs 1134	Stenberg, 2008
Risk of *Salmonella* infection	Cutting surface wood vs plastic	Not statistically significant: OR: 1.3, 95%CI [0.6;2.5] ¥ (p>0.05) £†	1, 115 vs 115	
	Using different surface for meat and non-meat vs same	Not statistically significant: OR: 0.9, 95%CI [0.5;1.5] ¥ (p>0.05) £†		
Risk of diarrhoea	Using separate chopping board for raw and cooked food vs same	Statistically significant: 999/1606 vs 860/1537 OR: 0.741, 95%CI [0.599;0.919] (p<0.05) *With benefit for using separate chopping board for raw and cooked food*	1, 1606 vs 1537	
	Using separate chopping board for raw and cooked meat vs same	Statistically significant: 807/1608 vs 688/1559 OR: 0.803, 95%CI [0.648;0.994] (p<0.05) *With benefit for using separate chopping board for raw and cooked meat*	1, 1608 vs 1559	
Risk of *E. coli* O157:H7 infection	Not washing hands after handling raw ground beef vs washing	Statistically significant: OR: 8.5, 95%CI [1.8;39.6] (p=0.004) £† *With harm for not washing hands after handling raw ground beef*	1, 23 vs 44	
Cleanliness in kitchen				
Risk of *Campylobacter* infection	Scalding cutting boards vs not	Not statistically significant: OR: 0.26, 95%CI [0.06;1.17] ¥ (p>0.05) £†	1, 217 vs 236	Stenberg, 2008
	Scalding sink vs not	Not statistically significant: OR: 0.82, 95%CI [0.10;6.71] ¥ (p>0.05) £†		
Risk of *Salmonella* infection	Cleaning chopping board between meat and non-meat vs not	Not statistically significant: OR: 3.7, 95%CI [0.3;44.9] ¥ (p>0.05) £†	1, 115 vs 115	
	Cleaning cutting surface with soap vs water	Not statistically significant: OR: 1.4, 95%CI [0.4;5.7] ¥ (p>0.05) £†		

Storage of food				
Risk of diarrhoea	Storing meat in refrigerator not on bottom shelf	Statistically significant: 740/1704 vs 837/1705 OR: 1.419, 95%CI [1.155;1.742] ($p<0.05$) *With harm for storing meat in refrigerator not on bottom shelf*	1, 1704 vs 1705	Stenberg, 2008

£ No raw data available

† Imprecision (lack of data)

¥ Imprecision (large variability of results)

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	-1	See systematic review
Imprecision	-1	Lack of data, large variability in results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low[D]**	

Conclusion	**Preparation of food** It was shown that the following risk factors resulted in a statistically significant increased risk of *E. coli* O157:H7 infection or risk of diarrhoea: frequently defrosting chicken in microwave and not washing hands after handling raw ground beef (Stenberg 2008). It was shown that the following risk factor resulted in a statistically significant decreased risk of diarrhoea: using a separate chopping board for raw and cooked food and using a separate chopping board for raw and cooked meat (Stenberg 2008). A statistically significant difference in the risk of *Salmonella* infection in case of using a wooden versus a plastic cutting surface and using a different surface for meat and non-meat could not be demonstrated (Stenberg 2008). Evidence is of very low quality and results cannot be considered precise due to lack of data and large variability of results. **Cleanliness in kitchen** A statistically significant decreased risk of *Salmonella* infection in case of the following risk factors could not be demonstrated: scalding cutting boards, scalding sink, cleaning the chopping board between meat and non-meat and cleaning the cutting surface with soap (versus water) (Stenberg 2008). Evidence is of very low quality and results cannot be considered precise due to lack of data and large variability of results. **Storage of food** It was shown that the following risk factor resulted in a statistically significant increased risk of diarrhoea: storing meat in refrigerator not on bottom shelf (Stenberg 2008). Evidence is of very low quality and results cannot be considered precise due to lack of data and large variability of results.
Reference(s)	**Systematic review** Stenberg A, Macdonald C, Hunter PR. *How effective is good domestic kitchen hygiene at reducing diarrhoeal disease in developed countries? A systematic review and reanalysis of the UK IID study*. BMC Public Health 2008, 8:71

Dehydration – Clinical signs/symptoms (diagnostics)

Question (PICO)	Among persons (P), are some symptoms (I) more predictive than others (C) for the diagnosis of dehydration (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. MeSH descriptor: [diarrhea] explode all trees or MeSH descriptor: [dehydration] explode all trees OR diarr*:ti,ab,kw OR dehydrat*:ti,ab,kw 2. MeSH descriptor: [sensitivity and specificity] explode all trees OR MeSH descriptor: [predictive value of tests] explode all trees OR MeSH descriptor: [reference values] explode all trees OR MeSH descriptor: [roc curve] explode all trees OR 'sensitivity':ti,ab,kw OR 'specificity':ti,ab,kw OR 'false positive':ti,ab,kw OR 'false negative':ti,ab,kw OR 'accuracy':ti,ab,kw OR 'predictive value':ti,ab,kw OR 'reference value':ti,ab,kw OR 'reference standard':ti,ab,kw OR 'roc':ti,ab,kw OR 'likelihood ratio':ti,ab,kw 3. signs:ti,ab,kw OR sign:ti,ab,kw OR symptom*:ti,ab,kw 4. MeSH descriptor: [meta-analysis] explode all trees OR meta analys*:ti,ab,kw OR meta-analys*:ti,ab,kw OR 'cochrane':ti,ab,kw OR 'embase':ti,ab,kw OR 'pubmed':ti,ab,kw OR 'medline':ti,ab,kw OR 'reference list':ti,ab,kw OR 'reference lists':ti,ab,kw OR 'bibliography':ti,ab,kw OR 'bibliographies':ti,ab,kw OR 'hand-search':ti,ab,kw OR 'manual search':ti,ab,kw OR 'selection criteria':ti,ab,kw OR 'relevant journals':ti,ab,kw 5. Systematic review (no time restriction): 1-4 AND 6. Individual experimental/observational studies (from 2008 until 2015): 1-3 AND **MEDLINE** (via PubMed interface) for guidelines and systematic reviews using the following search strategy: 1. "diarrhea"[Mesh] OR "dehydration"[Mesh] OR diarr*[TIAB] OR dehydrat*[TIAB] 2. signs[tiab] OR sign[tiab] OR symptom*[tiab] 3. "sensitivity and specificity"[Mesh] OR "sensitivity"[TIAB] OR "specificity"[TIAB] OR "predictive value of tests"[Mesh] OR "false positive"[TIAB] OR "false negative"[TIAB] OR "accuracy"[TIAB] OR "predictive value"[TIAB] OR "reference values"[Mesh] OR "reference value"[TIAB] OR"reference standard"[TIAB] OR "roc curve"[Mesh] OR "roc"[TIAB] OR "likelihood ratio"[TIAB] 4. "guideline "[Publication Type] OR "Practice Guidelines as Topic"[Mesh] OR "Practice Guideline "[Publication Type] OR practice guideline*[TIAB])) OR Meta-Analysis as Topic[Mesh] OR meta analy*[TIAB] OR metaanaly*[TIAB] OR Meta-Analysis[Publication Type] OR systematic review*[TIAB] OR systematic overview*[TIAB] OR Review Literature as Topic[Mesh] OR cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB])))) OR reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB] OR selection criteria[TIAB] OR data extraction[TIAB] 5. Systematic review (no time restriction): 1-4 AND 6. Individual experimental/observational studies (from 2008 until 2015): 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'diarrhea'/exp OR 'dehydration'/exp OR diarr:ab,ti OR dehydrat:ab,ti 2. 'signs':ab,ti OR 'sign':ab,ti OR symptom*:ab,ti 3. 'sensitivity and specificity'/exp OR 'sensitivity':ab,ti OR 'specificity':ab,ti OR 'false positive':ab,ti OR 'false negative':ab,ti OR 'diagnostic accuracy'/exp OR 'accuracy':ab,ti OR 'predictive value'/exp OR 'predictive value':ab,ti OR 'reference value'/exp OR 'reference value':ab,ti OR 'reference standard':ab,ti OR 'receiving operator characteristic'/exp OR 'receiver operating characteristic':ab,ti OR 'roc':ab,ti OR 'likelihood ratio':ab,ti

	4. 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti 5. Systematic review (no time restriction): 1-4 AND 6. Individual experimental/observational studies (from 2008 until 2015): 1-3 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	27 February 2015
In/Exclusion criteria	**Population:** Include: infants, children or adults that are dehydrated due to acute disease (e.g. diarrhoea). Exclude: infants, children or adults that are dehydrated due to chronic diseases (e.g. chronic kidney disease) **Intervention:** Include: clinical symptoms/signs suggestive for dehydration which can be detected by lay people (i.e. basic first responders, lay caregivers and/or community health workers). Exclude: clinical symptoms suggestive for dehydration which cannot be detected by lay people (i.e. basic first responders, lay caregivers and/or community health workers). **Comparison:** Include: a diagnostic reference method for the diagnosis of dehydration (e.g. biological testing, calculating osmolality (>295 mOsm/L)) Exclude: studies not using a diagnostic reference method. **Outcome:** Include: Patient-important outcomes (i.e. survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects)) or accuracy-related outcomes such as sensitivity, specificity and/or positive/negative likelihood ratio (pLR/nLR). Likelihood ratios were considered as the preferred measure of diagnostic accuracy since they are clinically more meaningful than sensitivities, specificities, or diagnostic odds ratios. They quantify how strongly the likelihood of a disease is changed by the presence (pLR) or absence (nLR) of a symptom or sign. A LR of 1 indicates a test result without any diagnostic value. LRs of 1 to 2 or 0.5 to 1 change the likelihood very little and they are rarely important. LRs ≤0.5 or ≥2 change it at least moderately and can be considered as clinically helpful in the context of medical history taking and physical examination. If no information on likelihood ratios is reported, data of sensitivity and specificity are extracted. **Study design:** Include: a systematic review (of diagnostic accuracy studies) was included if the search strategy and selection criteria are clearly described and if at least MEDLINE and one other relevant database was searched. If no systematic review was published within the last 5 years, a search for individual diagnostic accuracy studies was performed (from latest systematic review until search date). Exclude: case series**,** animal studies, *ex vivo* or *in vitro* studies. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline)

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Pruvost, 2008, France	Systematic review of 12 diagnostic accuracy studies	Young (1 month-5 years) non-malnourished children with a diagnosis of dehydration due to acute diarrhea (n=21-234, range): 3 studies were performed in an hospital setting, 7 in an emergency department for children, 2	Index test (symptom): -delayed skin recoloration time -skin fold -cold extremities -weak palpable radial pulse -no tears -dry mucosa -polypnea -sunken eyes	Dehydration was defined as a weight loss ≥5%

		in a department of gastroenterology.	-thirst -at least 3 clinical signs -2 among 4 clinical signs Reference standard: Anamnesis and/or clinical investigation and/or biological testing	
Shimizu, 2012, Japan	Diagnostics: accuracy study	Twenty-seven (16 male, 11 female) patients aged 65 or older who presented to an acute care teaching hospital and were consecutively admitted to the Department of Medicine with acute medical conditions. Patients excluded from the study were those with chronic kidney disease. The patients were diagnosed as having dehydration or not having dehydration.	Index test (symptom): -decreased consciousness level -dry axilla -dry mouth -sunken eyes -decreased skin turgor Reference standard: serum osmolality > 295 mOsm/L	
Steiner, 2004, USA	Systematic review of 26 diagnostic accuracy studies	Young infants and children (aged 1 month to 5 years) that appeared to address the evaluation of dehydration. We did not exclude articles if the study enrolled some children outside of that age range.	Index test: -abnormal skin turgor -abnormal respiratory pattern -sunken eyes -dry mucous membrane -cool extremities -weak pulse -absent tears -poor overall appearance Reference standard: difference between rehydration weight and the acute weight divided by the rehydration weight (examination signs or general dehydration assessment)	

Synthesis of findings

Outcome	**Index test vs reference standard**	**Effect Size**	**#studies, # participants**	**Reference**
Diagnosis dehydration: sensitivity/ specificity or positive likelihood ratio	Delayed skin recoloration time versus reference standard	Sensitivity: 44-96% Specificity: 94-100% †(no CI reported)	3, 491 (diagnostic accuracy study)	Pruvost, 2008
	Skin fold versus reference standard	Sensitivity: 35-65% Specificity: 56-97% †(no CI reported)	2, 327 (diagnostic accuracy study)	
	Cold extremities versus reference standard	Sensitivity: 10-11% Specificity: 93-100% †(no CI reported)	2, 206 (diagnostic accuracy study)	
		LR+ 1.5-18.8 (range), *index test can be considered as not*		Steiner, 2004

		clinically helpful for the presence of dehydration		
	Weak palpable radial pulse versus reference standard	Sensitivity: 4-25% Specificity: 86-100% †(no CI reported)	2, 360 (diagnostic accuracy study)	Pruvost, 2008
		LR+ 3.1-7.2 (range), *index test can be considered as not clinically helpful for the presence of dehydration*		Steiner, 2004
	Poor overall appearance	Sensitivity: 59-93% Specificity: 10-91% †(no CI reported)	3, 398 (diagnostic accuracy study)	Pruvost, 2008
		LR+ 1.90, 95% CI [0.97 to 3.8] *index test can be considered as not clinically helpful for the presence of dehydration*		Steiner, 2004
	No tears versus reference standard	Sensitivity: 43-100% Specificity: 33-89% †(no CI reported)		Pruvost, 2008
		LR+ 2.30, 95% CI [0.90 to 5.80] *index test can be considered as clinically helpful for the presence of dehydration*		Steiner, 2004
	Dry mucous membranes versus reference standard	Sensitivity: 80-100% Specificity: 49-78% †(no CI reported)		Pruvost, 2008
		LR+ 1.70, 95% CI [1.10 to 2.60] *index test can be considered as not clinically helpful for the presence of dehydration*	4, 533 (diagnostic accuracy study)	Steiner, 2004
	Dry axilla versus reference standard	Sensitivity: 44% Specificity: 89% †(no CI reported)	1, 27 (diagnostic accuracy study)	Shimizu, 2012
	Dry mouth versus reference standard	Sensitivity: 56% Specificity: 61% †(no CI reported)		
	Polypnea versus reference standard	Sensitivity: 43-50% Specificity: 74-86% †(no CI reported)	2, 327 (diagnostic accuracy study)	Pruvost, 2008
	Abnormal respiratory pattern versus reference standard	LR+ 2.00, 95% CI [1.50 to 2.70] *index test can be considered as clinically helpful for the presence of dehydration*	4, 581 (diagnostic accuracy study)	Steiner, 2004
	Sunken eyes versus reference standard	Sensitivity: 60-81% Specificity: 27-84% †(no CI reported)	3, 398 (diagnostic accuracy study)	Pruvost, 2008
		Sensitivity: 22% Specificity: 83% †(no CI reported)	1, 27 (diagnostic accuracy study)	Shimizu, 2012
		LR+ 1.70, 95% CI [1.10 to 2.50] *index test can be considered as not clinically helpful for the presence of dehydration*	4, 533 (diagnostic accuracy study)	Steiner, 2004

	Thirst versus reference standard	Sensitivity: 66% Specificity: 49% †(no CI reported)	1, 102 (diagnostic accuracy study)	Pruvost, 2008
	At least 3 clinical signs (decreased skin elasticity, poor overall appearance, no tears, abnormal respirations, dry mucous membranes, sunken eyes, abnormal radial pulse) versus reference standard	Sensitivity: 87% Specificity: 82% †(no CI reported)	1, 225 (diagnostic accuracy study)	
	2 among 4 clinical signs (delayed skin recoloration time, dry mucosa, no tears, poor overall appearance) versus reference standard	Sensitivity: 79% Specificity: 87% †(no CI reported)		
	Decreased consciousness level versus reference standard	Sensitivity: 11% Specificity: 72% †(no CI reported)	1, 27 (diagnostic accuracy study) §	Shimizu, 2012
	Decreased skin turgor	Sensitivity: 22% Specificity: 72% †(no CI reported)		
		LR+ 2.50, 95% CI [1.50 to 4.20] *index test can be considered as clinically helpful for the presence of dehydration*	5, 602 (diagnostic accuracy study)	Steiner, 2004

LR+: positive likelihood ratio (sensitivity/1-specificity)

† Imprecision (lack of data)

§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Information about 'limitations of study design' from the SR
Pruvost, 2008	Quality level of the included studies was considered as level 3 (Independent, blind comparison of test with a valid gold standard; patients enrolled in a non-consecutive fashion, using a subset or smaller group who may have had the condition and generated definitive results on both test and gold standard) or level 4 (Nonindependent comparison of a test with a valid gold standard among a "grab" sample of patients believed to have the condition in question)
Steiner, 2004	

Individual diagnostic accuracy studies

Author, Year	**Patient selection** (Was a consecutive or random sample of patients enrolled? Was a case–control design avoided? Did the study avoid inappropriate exclusions?)	**Index test** (Were the index test results interpreted without knowledge of the results of the reference standard? If a threshold was used, was it prespecified?)	**Reference standard** (Is the reference standard likely to correctly classify the target condition? Were the reference standard results interpreted without knowledge of the results of the index test?)	**Flow and Timing** (Was there an appropriate interval between index tests and reference standard? Did all patients receive a reference standard? Did all patients receive the same reference standard? Were all patients included in the analysis?)	**Other limitations**
Shimizu, 2012	yes	unclear, not specified in the article	yes	yes	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	0	
Inconsistency	0	
Indirectness	-1	Data from diagnostic accuracy studies (surrogate markers for patient important outcomes
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is limited evidence showing that at least 3 of the following clinical signs are predictive for the diagnosis of dehydration due to acute diarrhoea (best combination sensitivity/specificity): decreased skin elasticity, poor overall appearance, no tears, abnormal respirations (deep and rapid), dry mucous membranes, sunken eyes, abnormal radial pulse (weak/impalpable). Additionally, 2 among the following 4 clinical signs could also be considered as predictive for the diagnosis of dehydration (due to acute diarrhoea) (best combination sensitivity/specificity): delayed skin recoloration time, dry mucosa, no tears, poor overall appearance (Pruvost 2008). Evidence is of low quality.
Reference(s)	**Articles:** Pruvost I, Dubos F, Aurel M, Hue V, Martinot A. *Value of history and clinical and laboratory data for the diagnosis of dehydration due to acute diarrhea in children younger than 5 years.* Presse Med 2008, 37(4):600-609 Shimizu M, Kinoshita K, Hattori K, Ota Y, Kanai T, Kobayashi H, Tokuda Y. *Physical signs of dehydration in the elderly*. Intern Med 2012, 51(10):1207-1210 Steiner MJ, DeWalt DA, Byerley JS. *Is this child dehydrated?* JAMA 2004, 291(22):2746-2754

Dehydration – Oral rehydration solution (ORS) (First Aid)

Question (PICO)	In victims with diarrhea because of food poisoning (P) is intake of ORS (I) versus not (C) an effective method of rehydration (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 4. [mh diarrhea] OR [mh dehydration] OR diarr*:ti,ab,kw OR dehydrat*:ti,ab,kw 5. [mh "fluid therapy"] OR rehydr*:ti,ab,kw OR ORS:ti,ab,kw OR hydrat*:ti,ab,kw 6. #1 AND #2 **MEDLINE** (via PubMed interface) for guidelines and systematic reviews using the following search strategy: 5. "Diarrhea"[Mesh] OR "Dehydration"[Mesh] OR diarr*[TIAB] OR dehydrat*[TIAB] 6. "Fluid Therapy"[Mesh] OR "World Health Organization oral rehydration solution"[Supplementary Concept] OR "rehydration solutions"[Mesh] OR ORS[TIAB] OR hydrat*[TIAB] OR rehydr*[TIAB] 7. ((((((((((((Meta-Analysis as Topic[Mesh])) OR ((meta analy*[TIAB]))) OR ((metaanaly*[TIAB]))) OR ((Meta-Analysis[Publication Type]))) OR ((systematic review*[TIAB] OR systematic overview*[TIAB]))) OR ((Review Literature as Topic[Mesh])))) OR ((cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB]))) OR ((reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB]))) OR ((((selection criteria[TIAB] OR data extraction[TIAB])) AND ((Review[PT]))))))) NOT ((Comment[PT] OR Letter[PT] OR Editorial[PT] OR animal[Mesh] NOT (animal[Mesh] AND human[Mesh]))) 8. 1-3 AND **Embase** (via Embase.com interface) for guidelines and systematic reviews using the following search strategy: 5. 'Diarrhea'/exp OR 'Dehydration'/exp OR diarr*:ab,ti OR dehydrat*:ab,ti 6. 'oral rehydration therapy'/exp OR 'oral rehydration solution'/exp OR ORS:ab,ti OR hydrat*:ab,ti OR rehydr*:ab,ti 7. 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti 8. 1-3 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	20 February 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare.

	Outcome: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Hartling, 2006, Canada	Systematic review	17 studies (n=1811, aged 1 day to 18 years) performed in USA, Canada, Australia, Finland, Puerto Rico, Egypt, Mexico, Iran, Afghanistan, Colombia and Peru. All studies compared oral rehydration therapy (n=1015) vs intravenous therapy (n=796)	Intervention: ORS solutions containing glucose or dextrose, as well as sodium, potassium and chloride. Osmolarity ranged from 210-390 mmol/L. Control: IVT	Review declared as stable: given current evidence, new trials are unlikely to change the results, and further research on this question is not warranted.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Failure to rehydrate	ORT vs IVT	Statistically significant: 57/1004 vs 28/788 § RD: 0.04, 95%CI [0.01; 0.07] (p=0.018) *In favour of IVT*	18, 1004 vs 788	Hartling, 2006
Weight gain at discharge (g)		Not statistically significant: MD: -26.33, 95%CI [-206.92; 154.26] (p=0.78)	6, 189 vs 180 §	
Weight gain at discharge (%)		Not statistically significant: MD: -0.26, 95%CI [-1.56; 1.05] (p=0.70)	5, 419 vs 348	
Length of hospital stay (days)		Statistically significant: MD: -1.20, 95%CI [-2.38; -0.02] (p=0.046) *In favour of ORT*	6, 277 vs 249	
Incidences of hyponatremia		Not statistically significant: 18/160 vs 7/88 § RD: 0.01, 95%CI [-0.13; 0.15] (p=0.86)	2, 160 vs 88	
Incidences of hypernatremia		Not statistically significant: 1/611 vs 1/451 §	10, 611 vs 451	

		RD: 0.00, 95%CI [-0.01; 0.01] (p=1.0)		
Duration of diarrhea (h)		No statistically significant: MD: -5.90, 95%CI [-12.70; 0.89] (p=0.089)	8, 547 vs 413	
Total fluid intake (ml/kg) at 6h		Not statistically significant: MD: 32.09, 95%CI [-26.69; 90.88] (p=0.28)	8, 530 vs 455	
Total fluid intake (ml/kg) at 24h		Not statistically significant: MD: 73.45, 95%CI [-31.78; 178.69] (p=0.17)	7, 433 vs 402	
Total fluid intake (ml) at 6h		Not statistically significant: MD: 152.00, 95%CI [-64.21; 368.21] (p=0.17)*	1, 22 vs 15 §	
Complications: Paralytic ileus		Not statistically significant: 9/336 vs 0/334 § RD: 0.02, 95%CI [0.00; 0.05] (p=0.068)	2, 336 vs 334	
Complications: Pen-orbital edema		Not statistically significant: 12/460 vs 10/384 § RD: 0.00; 95%CI [-0.02; 0.02] (p=0.99)	7, 460 vs 384	
Complications: Abdominal distention		Not statistically significant: 1/236 vs 0/231 § RD: 0.02, 95%CI [0.00; 0.04] (p=0.070)	1, 236 vs 234	
Complications: Seizures		Not statistically significant: 3/475 vs 8/402 § RD: -0.01, 95%CI [-0.03; 0.01] (p=0.23)	6, 475 vs 402	
Sodium intake (mmol/kg) at 6h		Not statistically significant: MD: 5.80, 95%CI [-1.48; 13.07] (p=0.12)	3, 308 vs 299	
Sodium intake (mmol/kg) at 24h		Not statistically significant: MD: 1.25, 95%CI [-0.56; 3.07] (p=0.18)	7, 509 vs 483	

Mean ± SD (unless otherwise indicated)
RD: risk difference
* Calculations done by the reviewer(s) using Review Manager software
§ Imprecision (limited sample size or low number of events)

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See systematic review Hartling, 2006.
Imprecision	0	Although event size was low for some outcomes, we did not downgrade the level of evidence for imprecision (no variability in results, no lack of data, and no imprecision for 9 of the 16 outcomes)
Inconsistency	0	
Indirectness	-1	ORS vs IVT
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is limited evidence from 1 systematic review, including 17 studies, showing no difference between ORS (Oral Rehydration Solution) use and IVT (intravenous therapy). [In making this evidence conclusion, we place a higher value on the outcomes showing

	no significant difference between both interventions, than on the fact that there is a significant higher chance of failure to rehydrate with ORS compared to IVT, since ORS is more accessible than IVT, and IVT can still be started if ORS use fails)]. It was shown that ORT (Oral Rehydration Therapy) did not result in a statistically significant difference in weight gain, hyponatremia or hypernatremia, duration of diarrhoea or total fluid intake at 6 hours and 24 hours, compared to IVT. In addition, it was shown that ORS resulted in a statistically significant decrease of length of hospital stay compared to IVT. However, it was shown that ORS resulted in a statistically significant failure to rehydrate, compared to IVT. Evidence is of low quality.
Reference(s)	**Systematic reviews** Hartling L, Bellemare S, Wiebe N, Russell KF, Klassen TP, Craig WR. *Oral versus intravenous rehydration for treating dehydration due to gastroenteritis in children*. Cochrane Database of Systematic Reviews 2006, Issue 3. Art. No.:CD004390.

Dehydration – Reduced Osmolarity ORS (First Aid)

Question (PICO)	In victims with diarrhea because of food poisoning (P) is intake of reduced osmolarity ORS (I) versus standard WHO ORS (C) an effective method of rehydration (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh diarrhea] OR [mh dehydration] OR diarr*:ti,ab,kw OR dehydrat*:ti,ab,kw 2. [mh "fluid therapy"] OR rehydr*:ti,ab,kw OR ORS:ti,ab,kw OR hydrat*:ti,ab,kw 3. #1 AND #2 **MEDLINE** (via PubMed interface) for guidelines and systematic reviews using the following search strategy: 1. "Diarrhea"[Mesh] OR "Dehydration"[Mesh] OR diarr*[TIAB] OR dehydrat*[TIAB] 2. "Fluid Therapy"[Mesh] OR "World Health Organization oral rehydration solution"[Supplementary Concept] OR "rehydration solutions"[Mesh] OR ORS[TIAB] OR hydrat*[TIAB] OR rehydr*[TIAB] 3. ((((((((((Meta-Analysis as Topic[Mesh])) OR ((meta analy*[TIAB]))) OR ((metaanaly*[TIAB]))) OR ((Meta-Analysis[Publication Type]))) OR ((systematic review*[TIAB] OR systematic overview*[TIAB]))) OR ((Review Literature as Topic[Mesh])))) OR ((cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB]))) OR ((reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB]))) OR ((((selection criteria[TIAB] OR data extraction[TIAB])) AND ((Review[PT]))))) NOT ((Comment[PT] OR Letter[PT] OR Editorial[PT] OR animal[Mesh] NOT (animal[Mesh] AND human[Mesh]))) 4. 1-3 AND **Embase** (via Embase.com interface) for guidelines and systematic reviews using the following search strategy: 1. 'Diarrhea'/exp OR 'Dehydration'/exp OR diarr*:ab,ti OR dehydrat*:ab,ti 2. 'oral rehydration therapy'/exp OR 'oral rehydration solution'/exp OR ORS:ab,ti OR hydrat*:ab,ti OR rehydr*:ab,ti 3. 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR

	'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti 4. 1-3 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	20 February 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. Studies on use of ORS in patients with cholera. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Hahn, 2002, UK	Systematic review	14 studies (n=2251) in children (aged 0-36 months) with acute diarrhea performed in Egypt, Bangladesh, Mexico, Colombia, India, Panama and USA.	Intervention: reduced osmolarity ORS: total osmolarity ≤250 mmol/L Control: WHO standard oral rehydration solution: total osmolarity 311 mmol/L)	Cochrane systematic review. This Cochrane review is considered as historical question. No further update will be done. Reduced osmolarity ORS is considered as the standard according to the WHO.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Need for unscheduled intravenous fluid infusion	Reduced osmolarity ORS (stratified by sodium concentration) vs WHO standard ORS	Statistically significant: 88/967 vs 137/992 § OR: 0.59, 95%CI[0.45; 0.79] (p=0.00027) *In favour of reduced osmolarity ORS*	9, 967 vs 958	Hahn, 2002
Stool output	Reduced osmolarity ORS (stratified by sodium concentration) vs WHO standard ORS	Statistically significant: SMD: -0.20, 95%CI[-0.30; -0.10] (p=0.000092) *In favour of reduced osmolarity ORS*	7, 802 vs 789	
Episodes of vomiting during rehydration	Reduced osmolarity ORS (stratified by sodium concentration) vs WHO standard ORS	Statistically significant: 238/657 vs 275/648 § OR: 0.70, 95%CI[0.54; 0.91] (p=0.0073) *In favour of reduced osmolarity ORS*	7, 657 vs 648	
Presence of hyponatremia after rehydration	Reduced osmolarity ORS (stratified by sodium concentration) vs WHO standard ORS	Not statistically significant: 51/562 vs 36/609 § OR: 1.45, 95%CI[0.93; 2.26] ¥ (p=0.10)	6, 562 vs 609	

Mean ± SD (unless otherwise indicated)
¥ Imprecision (large variability of results)
§ Imprecision (low number of events)

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See systematic review Hahn, 2002
Imprecision	-1	Low number of events/large variability of the results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Moderate [B]**	

Conclusion	There is limited evidence from 1 systematic review, including 14 studies, in favour of reduced osmolarity ORS. It was shown that reduced osmolarity ORS resulted in a statistically significant decrease of unscheduled intravenous infusion, stool output and vomiting during rehydration, compared to standard WHO ORS. A statistically significant decrease of hyponatremia, using reduced osmolarity ORS compared to standard WHO ORS, could not be demonstrated (Hahn, 2002). Evidence is of moderate quality and results cannot be considered precise due to low number of events and large variability of results.
Reference(s)	**Systematic reviews** Hahn S, Kim Y, Garner P. *Reduced osmolarity oral rehydration solution for treating dehydration caused by acute diarrhoea in children*. Cochrane Database of Systematic Reviews 2002, Issue 1, Art. No.: CD002847.

Dehydration – Drinking carbonated drinks (First Aid)

Question (PICO)	In people with dehydration as a result of diarrhoea (P), is drinking cola or another carbonated drink (I) compared to not drinking or drinking water (O) an effective way to rehydrate (O)?
Search Strategy	Databases **Cochrane** for systematic reviews and controlled trials: 1. [mh "carbonated beverages"] OR "carbonated beverage*":ti,ab,kw OR "carbonated drink*":ti,ab,kw OR cola:ti,ab,kw OR "fizzy drink*":ti,ab,kw OR "soft drink*":ti,ab,kw 2. [mh Dehydration] or dehydration:ti,ab,kw OR dishydration:ti,ab,kw OR "fluid depletion":ti,ab,kw OR "fluid deprivation":ti,ab,kw OR "fluid loss":ti,ab,kw OR hypohydration:ti,ab,kw OR "water removal":ti,ab,kw OR "water stress":ti,ab,kw OR rehydration:ti,ab,kw OR [mh diarrhea] OR diarrhea:ti,ab,kw OR diarrheas:ti,ab,kw OR diarrhoea:ti,ab,kw OR diarrhoeas:ti,ab,kw OR hydration:ti,ab,kw 3. #1 AND #2 **Medline** via the Pubmed interface for systematic reviews, experimental and observational studies**:** 1. "carbonated beverages"[MeSH] OR carbonated beverage*[TIAB] OR carbonated drink*[TIAB] OR cola[TIAB] OR fizzy drink*[TIAB] OR soft drink*[TIAB] 2. Dehydration[MeSH] OR dehydration[TIAB] OR dishydration[TIAB] OR "fluid depletion"[TIAB] OR "fluid deprivation"[TIAB] OR "fluid loss"[TIAB] OR hypohydration[TIAB] OR "water removal"[TIAB] OR "Water stress"[TIAB] OR rehydration[TIAB] OR diarrhea[MeSH] OR diarrhea[TIAB] OR diarrheas[TIAB] OR diarrhoea[TIAB] OR diarrhoeas[TIAB] OR hydration[TIAB] 3. #1 AND #2 **Embase** via Embase.com for systematic reviews, experimental and observational studies: 1. 'carbonated beverage'/exp OR 'carbonated beverage':ab,ti OR 'carbonated beverages':ab,ti OR 'carbonated drink':ab,ti OR 'carbonated drinks':ab,ti OR cola:ab,ti OR 'fizzy drink':ab,ti OR 'fizzy drinks':ab,ti OR 'soft drink':ab,ti OR 'soft drinks':ab,ti 2. Dehydration/exp OR dehydration:ab,ti OR dishydration:ab,ti OR 'fluid depletion':ab,ti OR 'fluid deprivation':ab,ti OR 'fluid loss':ab,ti OR hypohydration:ab,ti OR 'water removal':ab,ti OR 'water stress':ab,ti OR 'rehydration':ab,ti OR diarrhea/exp OR diarrhea:ab,ti OR diarrheas:ab,ti OR diarrhoea:ab,ti OR diarrhoeas:ab,ti OR hydration:ab,ti 3. #1 AND #2 Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	13 January 2016
In/Exclusion criteria	**Population:** Include: Healthy volunteers, people with (signs of) dehydration due to diarrhoea. **Intervention:** Include: Oral ingestion of cola or other commercially available soft drinks. Exclude: Any other beverage. **Comparison:** Include: Oral ingestion of water or no intervention **Outcome:** Include: Hydration, measured by urine output, body mass, plasma volume, plasma and urine electrolyte balance. **Study design:** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available.

	An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: observational studies if intervention is already included in experimental studies, case series, cross-sectional studies, animal studies, ex vivo or in vitro studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year Country	Study design	Population	Comparison	Remarks
Brouns, 1998, The Netherlands	Experimental: Randomized controlled trial (within subjects design)	8 male subjects (aged 21.5(20.5-23.5)) were recruited for 3 different test conditions	Intervention: *Ad libitum* intake of a test drink (Coca Cola or an isotonic carbohydrate-electrolyte solution), following a dehydration protocol. Comparison: *Ad libitum* intake of water, following a dehydration protocol [only data of Coca Cola were extracted]	
Gonzàlez-Alonso, 1992, USA	Experimental: Randomized controlled trial (within subjects design)	10 subjects (aged 22.8±2.8) were recruited for 3 different test conditions	Intervention: Intake of a test drink (Diet Coke or a 6% carbohydrate-electrolyte solution) after a dehydration exercise. The volume ingested was equal to the amount lost during exercise (2.5% of BW). Comparison: Intake of water after the dehydration exercise. [only data of Diet Coke were extracted]	
Grandjean, 2000, USA	Experimental: Randomized controlled trial (within subjects design)	18 male healthy subjects (aged 28.7±4 years) were recruited for 5 different test conditions	Intervention: 35 mL/(kg x day) intake of different test drinks (equal amounts of water and Cola; equal amounts of water and Diet Coke; equal amounts of water, Cola, Diet Cola and instant Coffee; equal amounts of water and a non-caffeinated citrus soft drink). Comparison: Intake of 35 mL/(kg x day) of water. [only data of Cola and Diet Coke were extracted]	
Maughan, 2015, United Kingdom	Experimental: Randomized controlled trial	72 male healthy volunteers (aged 18-35 years), 15-17 subjects per condition tested	Intervention: Intake of 500 mL water, followed by 1 L of a test drink (sparkling water, Cola, Diet Coke, a sports drink, ORS, lager,	

	(within subjects design)	(max 4 conditions tested per subject and a total of 12 test conditions).	orange juice, coffee, tea, cold tea, full fat milk, skimmed milk), after an overnight fast. Comparison: Intake of 500 mL water, followed by 1L of water, after an overnight fast. [only data of Cola and Diet Coke were extracted]	
Tucker, 2015, USA	Experimental: Randomized controlled trial (within subjects design)	34 male subjects (aged 23.6±4.7 years) were recruited for 4 different test conditions	Intervention: 35 mL/(kg x day) intake of different test drinks (equal amounts of water and Cola; equal amounts of water and Diet Coke; equal amounts of water, Cola, Diet Coke and orange juice). Comparison: Intake of 35 mL/(kg x day) of water. [only data of Cola and Diet Coke were extracted]	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Rehydration in healthy volunteers				
Percentage rehydration in 2h	Diet Coke vs water	Statistically significant: 54±5% vs 64±5% MD: -10 £ (p<0.05) *In favour of water*	1, 10 vs 10 (within subjects design) §	Gonzàlez-Alonso, 1992
Fluid retention in 6h (L)	Cola vs water	Not statistically significant: 1.57[0.98-1.76] vs 1.26[1.08-1.39] MD: 0.31 £† (p>0.05)	1, 8 vs 8 (within subjects) §	Brouns, 1998
Urine parameters in healthy volunteers				
Cumulative urine production in 2h (mL)	Diet Coke vs water	Not statistically significant: 600±90 vs 710±100 MD: -110 £† (p>0.05)	1, 10 vs 10 (within subjects design) §	Gonzàlez-Alonso, 1992
Cumulative urine production in 4h (g)		Not statistically significant: 1200±150 vs 1300±150 λ MD: -100 £† (p>0.05)	1, 16 vs 16 (within subjects design)	Maughan, 2015
	Cola vs water	Not statistically significant: 1200±150 vs 1300±150 λ MD: -100 £† (p>0.05)	1, 17 vs 17 (within subjects design)	Maughan, 2015
Cumulative urine production in 6h (kg) (median [25-75 percentile])		Not statistically significant: 1 [0.82-1.2] vs 0.96 [0.4-1.49] MD: 0.04 £† (p>0.05)	1, 8 vs 8 (within subjects design) §	Brouns, 1998
Urine production over 24h (ml)		Not statistically significant: 1424±410 vs 1424±395 MD: 0 £† (p>0.05)	1, 18 vs 18 (within subjects design) §	Grandjean, 2000
		Not statistically significant: 1443±576 vs 1549±594 MD: 106 £† (p>0.05)	1, 34 vs 34 (within subjects design) §	Tucker, 2015
	Diet Coke vs water	Not statistically significant: 1403±431 vs 1424±395	1, 18 vs 18 (within subjects design) §	Grandjean, 2000

		MD: 21 £† (p>0.05)		
		Not statistically significant: 1690±668 vs 1549±594 MD: 141 £† (p>0.05)	1, 34 vs 34 (within subjects design) §	Tucker, 2015
Urine osmolality after 24h (mOsm/kg)	Cola vs water	Not statistically significant: 666.4±159.7 vs 664.9±200.4 MD: 1.5 £† (p>0.05)	1, 18 vs 18 (within subjects design) §	Grandjean, 2000
		Not statistically significant: 645±251 vs 613±209 MD: 32 £† (p>0.05)	1, 34 vs 34 (within subjects design) §	Tucker, 2015, USA
	Diet Coke vs water	Not statistically significant: 676.0±181.8 vs 664.9±200.4 MD: 11.1 £† (p>0.05)	1, 18 vs 18 (within subjects design) §	Grandjean, 2000
		Not statistically significant: 601±246 vs 613±209 MD: 12 £† (p>0.05)	1, 34 vs 34 (within subjects design) §	Tucker, 2015, USA
Urine specific gravity after 24h	Cola vs water	Not statistically significant: 1.018±0.005 vs 1.018±0.004 MD: 0 £† (p>0.05)	1, 18 vs 18 (within subjects design) §	Grandjean, 2000
		Not statistically significant: 1.019±0.008 vs 1.018±0.006 MD: 0.001 £† (p>0.05)	1, 34 vs 34 (within subjects design) §	Tucker, 2015
	Diet Coke vs water	Not statistically significant: 1.018±0.004 vs 1.018±0.004 MD: 0 £† (p>0.05)	1, 18 vs 18 (within subjects design) §	Grandjean, 2000
		Not statistically significant: 1.018±0.018 vs 1.018±0.006 MD: 0 £† (p>0.05)	1, 34 vs 34 (within subjects design) §	Tucker, 2015
Urine creatinine levels after 24h (mg/dL)	Cola vs water	Not statistically significant: 1982.3±401.6 vs 1996.7±285.3 MD: 14.4 £† (p>0.05)	1, 18 vs 18 (within subjects design) §	Grandjean, 2000
		Not statistically significant: 150.1±58.8 vs 146.7±56.8 MD: 3.4 £† (p>0.05)	1, 34 vs 34 (within subjects design) §	Tucker, 2015
	Diet Coke vs water	Not statistically significant: 1937.7±270.7 vs 1996.7±285.3 MD: 59 £† (p>0.05)	1, 18 vs 18 (within subjects design) §	Grandjean, 2000
		Not statistically significant: 132.4±56.4 vs 146.7±56.8 MD: 14.3 £† (p>0.05)	1, 34 vs 34 (within subjects design) §	Tucker, 2015
Urine Na^+ loss during 2h (mEq)	Diet Coke vs water	Not statistically significant: 60±12 vs 78±15 MD: 18 £† (p>0.05)	1, 10 vs 10 (within subjects design) §	Gonzàlez-Alonso, 1992
Urine Na^+ loss during 6h (mg) (median[25-75 percentile])	Cola vs water	Statistically significant: 1516 [770-1700] vs 1054[641-1186] MD: 462 £ (p<0.05) *In favour of water*	1, 8 vs 8 (within subjects design) §	Brouns, 1998
Urine Na^+ loss after 24h (mM)		Not statistically significant: 106.2±39.4 vs 98.3±41.3 MD: 7.9 £† (p>0.05)	1, 18 vs 18 (within subjects design) §	Grandjean, 2000
		Not statistically significant: 105.8±59.2 vs 99.2±51.8 MD: 6.6 £† (p>0.05)	1, 34 vs 34 (within subjects design) §	Tucker, 2015
	Diet Coke vs water	Not statistically significant: 103.5±39.3 vs 98.3±41.3 MD: 5.2 £† (p>0.05)	1, 18 vs 18 (within subjects design) §	Grandjean, 2000

		Not statistically significant: 81.4±40.5 vs 99.2±51.8 MD: 17.8 £† (p>0.05)	1, 34 vs 34 (within subjects design) §	Tucker, 2015
Urine Cl^- loss during 2h (mEq)		Not statistically significant: 97±15 vs 119±19 MD: 22 £† (p>0.05)	1, 10 vs 10 (within subjects design) §	Gonzàlez-Alonso, 1992
Urine Cl^- loss during 6h (mg)	Cola vs water	Not statistically significant: 2214[1431-2870] vs 1699[1583-2130] MD: 515 £† (p>0.05)	1, 8 vs 8 (within subjects design) §	Brouns, 1998
Urine Cl^- loss after 24h (mM)		Not statistically significant: 75.8±34.6 vs 69.2±37.4 MD: 6.6 £† (p>0.05)	1, 18 vs 18 (within subjects design) §	Grandjean, 2000
		Not statistically significant: 108±46.3 vs 105.6±46.1 MD: 2.4 £† (p>0.05)	1, 34 vs 34 (within subjects design) §	Tucker, 2015
	Diet Coke vs water	Not statistically significant: 75.1±34.6 vs 69.2±37.4 MD: 5.9 £† (p>0.05)	1, 18 vs 18 (within subjects design) §	Grandjean, 2000
		Not statistically significant: 87±29.2 vs 105.6±46.1 MD: 18.6 £† (p>0.05)	1, 34 vs 34 (within subjects design) §	Tucker, 2015
Urine K^+ loss during 2h (mEq)		Not statistically significant: 38±8 vs 57±14 MD: 19 £† (p>0.05)	1, 10 vs 10 (within subjects design) §	Gonzàlez-Alonso, 1992
Urine K^+ loss during 6h (mg)	Cola vs water	Not statistically significant: 902[488-1311] vs 1280[765-1598] MD: 378 £† (p>0.05)	1, 8 vs 8 (within subjects design) §	Brouns, 1998
Urine K^+ loss after 24h (mM)		Not statistically significant: 31.22±12.35 vs 29.33±13.81 MD: 1.89 £† (p>0.05)	1, 18 vs 18 (within subjects design) §	Grandjean, 2000
		Not statistically significant: 25.9±11.9 vs 25.2±12.9 MD: 0.7 £† (p>0.05)	1, 34 vs 34 (within subjects design) §	Tucker, 2015
	Diet Coke vs water	Not statistically significant: 30.28±13.39 vs 29.33±13.81 MD: 0.95 £† (p>0.05)	1, 18 vs 18 (within subjects design) §	Grandjean, 2000
		Not statistically significant: 20.9±13.4 vs 25.2±12.9 MD: 4.3 £† (p>0.05)	1, 34 vs 34 (within subjects design) §	Tucker, 2015
Urine Mg^{2+} loss during 6h (mg)	Cola vs water	Statistically significant: 86[68-105] vs 44[36-48] MD: 42 £ (p<0.05) *In favour of water*	1, 8 vs 8 (within subjects design) §	Brouns, 1998
Urine Ca^{2+} loss during 6h (mg) (median[25-75 percentile])		Statistically significant: 83[59-114] vs 49[33-57] MD: 34 £ (p<0.05) *In favour of water*	1, 8 vs 8 (within subjects design) §	Brouns, 1998
Whole body parameters				
Total body weight loss after 2h (g)	Diet coke vs water	Statistically significant: 230±20 vs 140±20 MD: 90 £ (p<0.05) *In favour of water*	1, 10 vs 10 (within subjects design) §	Gonzàlez-Alonso, 1992
Total body weight after 24h (kg)	Cola vs water	Not statistically significant: 76.5±12.6 vs 76.6±12.0 MD: 0.1 £† (p>0.05)	1, 34 vs 34 (within subjects design) §	Tucker, 2015
	Diet Coke vs water	Not statistically significant: 76.3±12.5 vs 76.6±12.0	1, 34 vs 34 (within subjects design) §	Tucker, 2015

		MD: 0.3 £† (p>0.05)		
Total body water after 24h (kg)	Cola vs water	Not statistically significant: 43.8±6 vs 43.9±5.9 MD: 0.1 £† (p>0.05)	1, 34 vs 34 (within subjects design) §	Tucker, 2015
	Diet Coke vs water	Not statistically significant: 43.7±6.1 vs 43.9±5.9 MD: 0.2 £† (p>0.05)	1, 34 vs 34 (within subjects design) §	Tucker, 2015
Intracellular body water after 24h (kg)	Cola vs water	Not statistically significant: 25.5±3 vs 25.6±2.6 MD: 0.1 £† (p>0.05)	1, 34 vs 34 (within subjects design) §	Tucker, 2015
	Diet Coke vs water	Not statistically significant: 25.5±3.1 vs 25.6±2.6 MD: 0.1 £† (p>0.05)	1, 34 vs 34 (within subjects design) §	Tucker, 2015
Extracellular body water after 24h (kg)	Cola vs water	Not statistically significant: 18.2±3 vs 18.3±3 MD: 0.1 £† (p>0.05)	1, 34 vs 34 (within subjects design) §	Tucker, 2015
	Diet Coke vs water	Not statistically significant: 18.1±3 vs 18.3±3 MD: 0.2 £† (p>0.05)	1, 34 vs 34 (within subjects design) §	Tucker, 2015
Blood parameters				
% Total blood volume after 2h	Diet Coke vs water	Not statistically significant: -2.6±0.9% vs -2.1±0.8% MD: 0.5 £† (p>0.05)	1, 10 vs 10 (within subjects design) §	Gonzàlez-Alonso, 1992
Serum osmolality after 2h (mOsm/kg)		Not statistically significant: 284±1 vs 285±1 λ MD: 1 £† (p>0.05)	1, 10 vs 10 (within subjects design) §	Gonzàlez-Alonso, 1992
Serum osmolality after 24h (mOsm/kg)	Cola vs water	Not statistically significant: 290.8±2.8 vs 291.7±2.7 MD: 0.9 £† (p>0.05)	1, 18 vs 18 (within subjects design) §	Grandjean, 2000
		Not statistically significant: 293±5 vs 291±4 MD: 2 £† (p>0.05)	1, 34 vs 34 (within subjects design) §	Tucker, 2015
	Diet Coke vs water	Not statistically significant: 291.8±2.8 vs 291.7±2.7 MD: 0.1 £† (p>0.05)	1, 18 vs 18 (within subjects design) §	Grandjean, 2000
		Not statistically significant: 292±5 vs 291±4 MD: 1 £† (p>0.05)	1, 34 vs 34 (within subjects design) §	Tucker, 2015
Serum hemoglobin after 24h (g/dL)	Cola vs water	Not statistically significant: 14.9±0.9 vs 14.8±1 MD: 0.1 £† (p>0.05)	1, 18 vs 18 (within subjects design) §	Grandjean, 2000
		Not statistically significant: 14.7±0.8 vs 14.8±0.9 MD: 0.1 £† (p>0.05)	1, 34 vs 34 (within subjects design) §	Tucker, 2015
	Diet Coke vs water	Not statistically significant: 14.7±0.9 vs 14.8±1 MD: 0.1 £† (p>0.05)	1, 18 vs 18 (within subjects design) §	Grandjean, 2000
		Not statistically significant: 14.7±0.8 vs 14.8±0.9 MD: 0.1 £† (p>0.05)	1, 34 vs 34 (within subjects design) §	Tucker, 2015
Serum % hematocrit after 24h	Cola vs water	Not statistically significant: 43.5±2.6% vs 43.4±2.5% MD: 0.1 £† (p>0.05)	1, 18 vs 18 (within subjects design) §	Grandjean, 2000
		Not statistically significant: 44.7±2.4% vs 45.1±2.6% MD: 0.4 £† (p>0.05)	1, 34 vs 34 (within subjects design) §	Tucker, 2015

	Diet Coke vs water	Not statistically significant: 43.5±2.3% vs 43.4±2.5% MD: 0.1 £† (p>0.05)	1, 18 vs 18 (within subjects design) §	Grandjean, 2000
		Not statistically significant: 44.8±2.4% vs 45.1±2.6% MD: 0.3 £† (p>0.05)	1, 34 vs 34 (within subjects design) §	Tucker, 2015
Serum Na^+ after 24h (mM)	Cola vs water	Not statistically significant: 141.8±1.4 vs 141.6±1.8 MD: 0.2 £† (p>0.05)	1, 18 vs 18 (within subjects design) §	Grandjean, 2000
		Not statistically significant: 141.6±1.9 vs 141.1±1.4 MD: 0.5 £† (p>0.05)	1, 34 vs 34 (within subjects design) §	Tucker, 2015
	Diet Coke vs water	Not statistically significant: 142±1.6 vs 141.6±1.8 MD: 0.4 £† (p>0.05)	1, 18 vs 18 (within subjects design) §	Grandjean, 2000
		Not statistically significant: 141.1±1.7 vs 141.1±1.4 MD: 0 £† (p>0.05)	1, 34 vs 34 (within subjects design) §	Tucker, 2015
Serum Cl^- after 24h (mM)	Cola vs water	Not statistically significant: 102.9±1.2 vs 102.8±1.8 MD: 0.1 £† (p>0.05)	1, 18 vs 18 (within subjects design) §	Grandjean, 2000
		Not statistically significant: 102.9±1.8 vs 102.9±1.6 MD: 0 £† (p>0.05)	1, 34 vs 34 (within subjects design) §	Tucker, 2015
	Diet Coke vs water	Not statistically significant: 102.9±1.2 vs 102.8±1.8 MD: 0.1 £† (p>0.05)	1, 18 vs 18 (within subjects design) §	Grandjean, 2000
		Not statistically significant: 102.6±1.6 vs 102.9±1.6 MD: 0.3 £† (p>0.05)	1, 34 vs 34 (within subjects design) §	Tucker, 2015
Serum K^+ after 24h (mM)	Cola vs water	Not statistically significant: 3.84±0.2 vs 3.84±0.24 MD: 0 £† (p>0.05)	1, 18 vs 18 (within subjects design) §	Grandjean, 2000
		Not statistically significant: 4.4±0.4 vs 4.3±0.4 MD: 0.1 £† (p>0.05)	1, 34 vs 34 (within subjects design) §	Tucker, 2015
	Diet Coke vs water	Not statistically significant: 3.84±0.16 vs 3.84±0.24 MD: 0 £† (p>0.05)	1, 18 vs 18 (within subjects design) §	Grandjean, 2000
		Not statistically significant: 4.3±0.3 vs 4.3±0.4 MD: 0 £† (p>0.05)	1, 34 vs 34 (within subjects design) §	Tucker, 2015
Serum Urea nitrogen after 24h (mg/dL)	Cola vs water	Not statistically significant: 15±3.5 vs 15.1±2.7 MD: 0.1 £† (p>0.05)	1, 18 vs 18 (within subjects design) §	Grandjean, 2000
		Not statistically significant: 14.7±2.8 vs 14.8±3.1 MD: 0.1 £† (p>0.05)	1, 34 vs 34 (within subjects design) §	Tucker, 2015
	Diet Coke vs water	Not statistically significant: 15.3±3.6 vs 15.1±2.7 MD: 0.2 £† (p>0.05)	1, 18 vs 18 (within subjects design) §	Grandjean, 2000
		Not statistically significant: 14.9±2.3 vs 14.8±3.1 MD: 0.1 £† (p>0.05)	1, 34 vs 34 (within subjects design) §	Tucker, 2015
Serum creatinine after 24h (mg/dL)	Cola vs water	Not statistically significant: 1.01±0.1 vs 1±0.11 MD: 0.01 £† (p>0.05)	1, 18 vs 18 (within subjects design) §	Grandjean, 2000

		Not statistically significant: 1.56±0.2 vs 1.5±0.2 MD: 0.06 £† (p>0.05)	1, 34 vs 34 (within subjects design) §	Tucker, 2015
	Diet Coke vs water	Not statistically significant: 1.01±0.096 vs 1±0.11 MD: 0.01 £† (p>0.05)	1, 18 vs 18 (within subjects design) §	Grandjean, 2000
		Not statistically significant: 1.56±0.22 vs 1.5±0.2 MD: 0.06 £† (p>0.05)	1, 34 vs 34 (within subjects design) §	Tucker, 2015
Serum protein after 24h (g or µg/dL)	Cola vs water	Not statistically significant: 7.8±0.3 vs 7.8±0.2 MD: 0 £† (p>0.05)	1, 18 vs 18 (within subjects design) §	Grandjean, 2000
		Not statistically significant: 6.94±0.96 vs 6.86±1.14 MD: 0.8 £† (p>0.05)	1, 34 vs 34 (within subjects design) §	Tucker, 2015
	Diet Coke vs water	Not statistically significant: 7.8±0.3 vs 7.8±0.2 MD: 0 £† (p>0.05)	1, 18 vs 18 (within subjects design) §	Grandjean, 2000
		Not statistically significant: 7.11±1.02 vs 6.86±1.14 MD: 0.25 £† (p>0.05)	1, 34 vs 34 (within subjects design) §	Tucker, 2015

Mean ± SD (unless otherwise indicated)
£ No CI available
† Imprecision (lack of data)
§ Imprecision (limited sample size or low number of events)
λ data extracted from graph

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Maughan, 2015	No: Randomized via online tool	Yes (obvious due to the nature of the intervention)	No	Yes, only urine volume reported, while urine osmolality & serum osmolality were also measured	Within subjects design
Gonzàlez-Alonso, 1992	Unclear: No info on randomization or allocation	Yes (obvious due to the nature of the intervention)	No	No	Within subjects design
Tucker, 2015	Unclear: Randomized, but without info on how randomization took place	Yes (obvious due to the nature of the intervention, although drinks were provided in unmarked bottles)	Yes, several outcome parameters were analysed on less than 34 participants, without accounting for	No	Within subjects design
Grandjean, 2000	Unclear: Randomized, but without info on how randomization took place	Yes (obvious due to the nature of the intervention, although drinks were provided in unmarked bottles)	No	No	Within subjects design

Brouns, 1998	Unclear: Randomized, but without info on how randomization took place	Yes (obvious due to the nature of the intervention)	No	No	Within subjects design

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	see table 'Quality of studies'
Imprecision	-1	4/5 studies report no power analysis and have low subject numbers + all studies are within subjects design, making an estimation of variability impossible
Inconsistency	0	
Indirectness	0	
Publication bias	-1	2/5 studies are sponsored by Coca Cola
QUALITY (GRADE)	**Final grading Very Low [D]**	

Conclusion(s)	There is limited evidence neither in favour of drinking carbonated beverages nor drinking water: A statistically significant increase in fluid retention, total body water, extracellular or intracellular body water, total blood volume, serum osmolality, serum haemoglobin, serum haematocrit, serum Na^+, Cl^-, K^+ levels, serum urea nitrogen levels, serum creatinine levels or serum protein levels using carbonated beverages compared to water, could not be demonstrated (Brouns 1998, Gonzàlez-Alonso 1992, Grandjean 2000, Tucker 2015). A statistically significant decrease in urine production, urine osmolality, urine specific gravity, urine creatinine levels, urine Na^+, Cl^- or K^+ loss or total body weight using carbonated beverages compared to water, could not be demonstrated (Brouns 1998; Gonzàlez-Alonso 1992; Grandjean 2000; Maughan 2015; Tucker 2015). However, it was shown that carbonated beverages resulted in a statistically significant increase in urinary Na^+ loss, urine Ca^{2+} loss and urine Mg^{2+} loss, compared to water (Brouns 1998). Furthermore, it was shown that carbonated beverages resulted in a statistically significant decrease in total body weight and rehydration, compared to water (Gonzàlez-Alonso, 1992). Evidence is of very low quality and results of these studies are imprecise due to limited sample size and lack of data.
Reference(s)	**Articles** Brouns F, Kovacs EM, Senden JM. *The effect of different rehydration drinks on post-exercise electrolyte excretion in trained athletes.* Int J Sports Med. 1998 Jan;19(1):56-60. González-Alonso J, Heaps CL, Coyle EF. *Rehydration after exercise with common beverages and water.* Int J Sports Med. 1992 Jul;13(5):399-406. Grandjean AC, Reimers KJ, Bannick KE, Haven MC. *The effect of caffeinated, non-caffeinated, caloric and non-caloric beverages on hydration.* J Am Coll Nutr. 2000 Oct;19(5):591-600. Maughan RJ, Watson P, Cordery PA, Walsh NP, Oliver SJ, Dolci A, Rodriguez-Sanchez N, Galloway SD. *A randomized trial to assess the potential of different beverages to affect hydration status: development of a beverage hydration index.* Am J Clin Nutr. 2015 Dec 23. pii: ajcn114769. [Epub ahead of print] Tucker MA, Ganio MS, Adams JD, Brown LA, Ridings CB, Burchfield JM, Robinson FB, McDermott JL, Schreiber BA, Moyen NE, Washington TA, Bermudez AC, Bennett MP, Buyckx ME. *Hydration Status over 24-H Is Not Affected by Ingested Beverage Composition.* J Am Coll Nutr. 2015;34(4):318-27.

Dehydration – Breast feeding (First Aid/Prevention)

Question (PICO)	In children (P), is a higher frequency/volume of breast feeding (I), compared to a lower frequency/volume of breastfeeding (C), effective for (prevention of) dehydration (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search term: 1. [mh Dehydration] OR dehydration:ti,ab 2. [mh "Breast feeding"] OR breastfeeding:ti,ab OR "breast feeding":ti,ab 3. 1-2 AND **MEDLINE** (via PubMed interface) for guidelines and systematic reviews using the following search strategy: 1. Dehydration[Mesh] OR dehydration[TIAB] 2. Breast feeding[Mesh] OR "breastfeeding"[TIAB] OR "breast feeding"[TIAB] 3. 1 AND 2 **Embase** (via Embase.com interface) using the following search strategy: 1. dehydration/exp OR dehydration:ab,ti 2. 'breast feeding'/exp OR breastfeeding:ab,ti OR 'breast feeding':ab,ti 3. 1 AND 2 Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	24 August 2015
In/Exclusion criteria	**Population**: Include: children normally receiving breast feeding **Intervention**: Include: stopping breast feeding, higher or lower frequency/volume of breastfeeding (e.g. ORS+breast feeding vs ORS) Exclude: breast feeding only vs no breast feeding **Outcome:** Include: (risk of) diarrhoea, dehydration; only data from multivariate analysis were extracted, i.e. data that were adjusted for confounding variables (e.g. …); Exclude: (risk of) hospital admission, chronic diarrhoea, data from univariate analysis (unadjusted) Design: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study (taking into account confounding variables at the analysis phase), controlled before and after study or controlled interrupted time series, and the data are available. Exclude: observational studies not taking into account confounding variables at the analysis phase, conference abstracts, case series, cross-sectional studies (studies collecting information concerning type of car and injury in health insurance companies), animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Remark**: a 1996 paper (Fuchs, 1996) was excluded since the study was also reported in a 2002 paper, however the latter contained more data and thus was included; a 1993 paper (Faruque, 1993) was excluded since the study was also reported in a 1992 paper, however the latter specifically focused on breast feeding and thus was included.

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Battacharya, 1995, India	Observational: case-control study	Cases (n=243): children admitted to the hospital with diarrhoea who were assessed as having severe or moderate dehydration. Moderate or severe dehydration was diagnosed when a child had definite signs of reduced skin elasticity and, in addition, had one or more of the following: sunken eyes, rapid and weak pulse, sunken anterior fontanel (provided open), and no urine for at least 6 h. Controls (n=136): children admitted to the hospital with diarrhoea who had mild or no dehydration. The child was assessed as having no or mild dehydration when there were no clear signs of dehydration with or without thirst.	Multiple risk factors, but only data on breastfeeding were extracted.	An interview with the mother was performed. Stepwise multiple logistic regression analysis was performed.
Faruque, 1992, Bangladesh	Observational: case-control study	Cases (n=285): children aged between 1 and 35 months with acute watery diarrhoea of six days or less, with moderate or severe dehydration (definite decreased skin elasticity and one or more of four signs: sunken eyes, failure to urinate for six hours, sunken anterior fontanel, and rapid and weak pulse) Controls (n=728): children aged between 1 and 35 months with diarrhoea without dehydration	Risk factors: Withdrawal of breast feeding, use of oral rehydration therapy [only data about breast feeding were extracted]	The case-control design required a sample size of 200 in each study group (with α=0.05, power of 90%, and odds ratio of 2). A field tested, structured, interviewer administered questionnaire was used by trained interviewers. A multivariate analysis was performed.
Fuchs, 2002, Brazil	Observational: case-control study	Dehydrating cases (n=192): children aged 0-23 months with an episode of acute diarrhoea (less than eight days duration) and presence of a persistent skinfold plus at least one of the following signs: sunken fontanel, dry mouth and tongue, sunken eyes, reduced urinary output, weak	Multiple risk factors, but only data on breastfeeding were extracted.	Diarrhoea was defined as: three or more loose or watery bowel movements within 24 hours for children older than 3

		pulse, drowsiness, or irritability. Mild diarrhoea cases (n=192): children with diarrhoea in the seven days preceding the interview and without signs of dehydration. Controls (n=192): children identified in the same neighbourhood and from the same age bracket as dehydrating diarrhoea cases, who had not presented diarrhoea in the preceding seven days.		months or according to the mother's report of more frequent and poorly formed stools (as compared to normal) for younger children. Standardized interviews with mothers or caretakers were performed. A conditional logistic regression analysis was performed.
Khin, 1985, Myanmar	Experimental: randomized controlled trial	52 children aged 6-24 months admitted to the paediatric wards of the Infectious Diseases Hospital for acute watery diarrhoea of less than 48 hours duration with grade II (moderate or severe) dehydration, who had been normally breast fed	Intervention: breast feeding plus oral rehydration solution Control: oral rehydration solution alone	Correct trial size was calculated using data from previous studies according to variable of response used
Zodpey, 1998, India	Observational: case-control study	Cases (n=387): children < 5 yrs, diagnosed with diarrhoea and severe or moderate dehydration (signs of reduced skin elasticity and one or more of the following: sunken eyes, rapid and weak pulse, sunken anterior fontanel, no urine output for the last six hours. Controls (n=387): children with diarrhoea, but without dehydration	Multiple risk factors, but only data on breastfeeding were extracted.	With an α error of 0.05 and 90% power, the sample size was calculated to be 387 cases with an equal number of controls. An interview with the mother was conducted by a trained interviewer. A multiple logistic regression analysis was performed.

Synthesis of findings

Outcome	Risk factor	Effect Size	#studies, # participants	Reference
Risk of dehydrating diarrhoea	Stopping breast feeding vs not	Statistically significant: OR: 6.4, 95%CI [2.3;17.3] (p<0.001) £† *With harm for stopping breast feeding*	1, 192 vs 192	Fuchs, 2002
		Statistically significant: OR: 2.5, 95%CI [1.2;5.0]	1, 192 vs 192	Fuchs, 2002

Risk of diarrhoea evolving in dehydration		(p=0.02) £† *With harm for stopping breast feeding*		
		Statistically significant: OR: 3.61, 95%CI [2.11;6.16] (p=0.000) £ *With harm for stopping breast feeding*	1, 387 vs 387 (power analysis)	Zodpey, 1998
		Statistically significant: OR: 5.23, 95%CI [1.37;19.99] (p=0.016) £ *With harm for stopping breast feeding*	1, 285 vs 728 (power analysis)	Faruque, 1992
Risk of diarrhoea evolving in moderate or severe dehydration		Statistically significant: OR: 6.8, 95%CI [3.8;12.2] (p<0.00001) £† *With harm for stopping breast feeding*	1, 243 vs 136	Battacharya, 1995
Stool output (ml/kg/patient)	ORS + breast feeding vs ORS alone	Not statistically significant: 89.2 ± 51 vs 115.8 ± 73.9 MD: -26.60, 95%CI [-61.11;7.91] ¥ (p=0.13) *	1, 26 vs 26 (power analysis)	Khin, 1985
No of times stools passed in hospital		Statistically significant: 12.1 ± 5.6 vs 17.4 ± 11.7 MD: -5.30, 95%CI [-10.29;-0.31] (p=0.04) * *In favour of ORS + breast feeding*		
Vomitus volume (ml/patient)		Not statistically significant: 22.9 ± 55.6 vs 15.2 ± 43.3 MD: 7.70, 95%CI [-19.39;34.79] ¥ (p=0.58) *		
Duration of diarrhoea in hospital (hours)		Not statistically significant: 43.3 ± 25.9 vs 45.7 ± 19.9 MD: -2.40, 95%CI [-14.95;10.15] (p=0.71) *		
Total ORS required for rehydration (ml/patient)		Statistically significant: 1570.4 ± 573.6 vs 2119.2 ± 979.5 MD: -548.80, 95%CI [-985.11;-112.49] (p=0.01) * *In favour of ORS + breast feeding*		

Mean ± SD (unless otherwise indicated); SD was calculated from SE by the reviewer

* Calculations done by the reviewer(s) using Review Manager software

£ No raw data available

† Imprecision (lack of data)

§ Imprecision (low number of events or limited sample size)

¥ Imprecision (large variability of results)

Stopping breast feeding

Quality of evidence

Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations
Battacharya, 1995	Unclear (no information about matching)	No	No (multivariable analysis)	No	
Faruque, 1992	Unclear (no information about matching)	No	No (multivariable analysis)	No	
Fuchs, 2002	No (matched cases and controls)	No	No (multivariable analysis)	No	
Zodpey, 1998	Unclear (no information about matching)	No	No (multivariable analysis)	No	

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	0	
Imprecision	-1	Lack of data
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low[D]**	

ORS + breast feeding vs ORS alone

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Khin, 1985	Unclear (randomization: random numbers were used; no information about allocation concealment)	Unclear (no information)	No	No	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	
Imprecision	-1	Large variability in results (for non-significant outcomes)
Inconsistency	0	
Indirectness	-1	Indirect outcomes for dehydration
Publication bias	0	
QUALITY (GRADE)	**Final grading Moderate [B] - Low[C]**	

Conclusion	Stopping breast feeding

	It was shown that withdrawing breast feeding resulted in a statistically significant increased risk of dehydrating diarrhoea, or risk of diarrhoea evolving in (moderate and severe) dehydration (Fuchs 2002, Zodpey 1998, Battacharya 1995, Faruque 1992). Evidence is of very low quality and results cannot be considered precise due to lack of data. **ORS + breast feeding vs ORS alone** There is evidence in favour of giving ORS and breast feeding. It was shown that ORS + breast feeding resulted in a statistically significant decreased number of times stools passed in hospital and total ORS required for rehydration compared to giving only ORS (Khin 1985). A statistically significant decrease of stool output, vomitus volume and duration of diarrhoea when giving ORS + breast feeding compared to ORS alone could not be demonstrated (Khin 1985). Evidence is of moderate/low quality. Non-significant results cannot be considered precise due to large variability in results.
Reference(s)	**Articles** Bhattacharya SK, Bhattacharya MK, Manna B, Dutta D, Deb A, Dutta P, Goswami AG, Dutta A, Sarkar S, Mukhopadhaya A, et al. *Risk factors for development of dehydration in young children with acute watery diarrhoea: a case-control study*. Acta Paediatr 1995, 84(2):160-4 Faruque AS, Mahalanabis D, Islam A, Hoque SS, Hasnat A. *Breast feeding and oral rehydration at home during diarrhoea to prevent dehydration*. Arch Dis Child 1992 Aug;67(8):1027-9. Fuchs SC, Victora CG. *Risk and prognostic factors for diarrheal disease in Brazilian infants: a special case-control design application*. Cad Saude Publica 2002, 18(3):773-82 Khin MU, Nyunt-Nyunt-Wai, Myo-Khin, Mu-Mu-Khin, Tin U, Thane-Toe. *Effect on clinical outcome of breast feeding during acute diarrhoea*. BMJ 1985, 290(6468): 587 Zodpey SP, Deshpande SG, Ughade SN, Hinge AV, Shirikhande SN. *Risk factors for development of dehydration in children aged under five who have acute watery diarrhoea: a case-control study*. Public Health 1998, 112(4):233-6

Hiccup – Techniques to stop hiccups (First Aid)

Question (PICO)	In people with hiccup (P), are certain techniques to stop hiccups (I) compared to doing nothing effective to stop hiccups (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search term: [mh "Hiccup"] OR hiccup*:ti,ab,kw **MEDLINE** (via PubMed interface) for guidelines and systematic reviews using the following search strategy: 1. "Hiccup"[Mesh] OR hiccup*[TIAB] OR singultus[TIAB] 2. "Ice"[Mesh] OR "Acetic Acid"[Mesh] OR "Breathing Exercises"[Mesh] OR "Valsalva maneuver"[Mesh] OR ice[TIAB] OR vinegar[TIAB] OR acetic acid[TIAB] OR sugar[TIAB] OR scar*[TIAB] OR lemon[TIAB] OR breathing[TIAB] OR Valsalva[TIAB] 3. 1 AND 2 **Embase** (via Embase.com interface) using the following search strategy: 1. 'hiccup'/exp OR hiccup*:ab,ti OR singultus:ab,ti 2. 'ice'/exp OR 'acetic acid'/exp OR 'breathing exercise'/exp OR 'Valsalva maneuver'/exp OR ice:ab,ti OR vinegar:ab,ti OR 'acetic acid':ab,ti OR sugar:ab,ti OR scar*:ab,ti OR lemon:ab,ti OR breathing:ab,ti OR Valsalva:ab,ti 3. 1 AND 2

Search date	25 August 2015
In/Exclusion criteria	**Population**: Include: people with acute hiccups; Exclude: persistent hiccups (lasting more than 48 hours) **Intervention**: Include: techniques to stop hiccups on a short term, including sucking an ice cube, sucking a sugar cube with vinegar, chewing a piece of lemon, stop breathing, scaring someone with hiccups, the Valsalva manoeuvre; Exclude: acupuncture, long term treatments **Outcome**: Include: stopping of hiccups **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: conference abstracts, case series, cross-sectional studies (studies collecting information concerning type of car and injury in health insurance companies)**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline)

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Hiccups – Pharyngeal stimulation (First Aid)

Question (PICO)	In humans with hiccups (P), is pharyngeal stimulation (I) compared to no pharyngeal stimulation (C) effective to stop hiccups (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search term: 1. [mh "Hiccup"] OR hiccup*:ti,ab,kw OR singultus*:ti,ab,kw 2. pharyn*:ti,ab 3. #1AND#2 **MEDLINE** (via PubMed interface) for guidelines and systematic reviews using the following search strategy: 1. "Hiccup"[Mesh] OR hiccup*[TIAB] OR singultus[TIAB] 2. "Pharynx"[Mesh] OR pharyn*[TIAB] 3. 1 AND 2 **Embase** (via Embase.com interface) using the following search strategy: 1. 'hiccup'/exp OR hiccup*:ab,ti OR singultus:ab,ti 2. 'pharynx'/exp OR pharyn*:ab,ti 3. 1 AND 2
Search date	11 January 2016
In/Exclusion criteria	**Population**: Include: people with hiccups (acute or persistent) **Intervention**: Include: stimulation of the pharynx. Exclude: pharyngeal stimulation through the nose. **Outcome**: Include: stopping of hiccups **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: conference abstracts, case series, cross-sectional studies (studies collecting information concerning type of car and injury in health insurance companies), animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Swallowing a foreign object – Inspection faeces (First Aid)

Question (PICO)	In people who have a swallowed a foreign object (P) is watchful waiting (I) better than early active removal (C) at achieving safe coin passage (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh foreign bodies] OR 'foreign body':ti,ab,kw OR 'foreign bodies':ti,ab,kw OR coin*:ti,ab,kw 2. [mh eating] OR [mh feeding behavior] OR eat*:ti,ab,kw OR ingest*:ti,ab,kw 3. Esophag*:ti,ab,kw OR oesophag*:ti,ab,kw 4. Watch*:ti,ab,kw OR observ*:ti,ab,kw OR inspect*:ti,ab,kw 5. 1-4 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Foreign bodies[Mesh] OR "foreign body"[TIAB] OR "foreign bodies"[TIAB] OR coin*[TIAB] 2. Eating[Mesh] OR "feeding behavior"[Mesh] OR eat*[TIAB] OR ingest*[TIAB] 3. Esophag*[TIAB] OR oesophag*[TIAB] 4. Watch*[TIAB] OR observ*[TIAB] OR inspect*[TIAB] 5. 1-4 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'Foreign body'/exp OR 'foreign body':ab,ti OR 'foreign bodies':ab,ti OR coin*:ab,ti 2. Eating/exp OR 'feeding behavior'/exp OR eat*:ab,ti OR ingest*:ab,ti 3. Esophag*:ab,ti OR Oesophag*:ab,ti 4. Watch*:ab,ti OR observ*:ab,ti OR inspect*:ab,ti 5. 1-4 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	03 September 2015
In/Exclusion criteria	**Population:** Include: people who have a swallowed a foreign object **Intervention:** Include: watchful waiting **Comparison:** Include: endoscopic removal (surgery) **Outcome:** Include: Outcomes related to spontaneous passage of the foreign object **Study design:** Include: a systematic review was included if the search strategy and selection criteria are clearly described and if at least MEDLINE and one other relevant database was searched. If no systematic review was published within the last 5 years, a search for individual experimental/observational studies was performed (from 2008-2015). Exclude: case series**,** cross-sectional studies, animal studies, *ex vivo* or *in vitro* studies. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year:** All years.

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Waltzman, 2005, USA	Experimental: randomized controlled trial	168 children who presented with oesophageal coins lodged in the oesophagus and who	Intervention: observation (with repeat radiographs ~16 hours after the initial image.)	With a sample size of 30 subjects per group, using Fisher's exact test with a .05 2-sided

		were observed (n=30, age: 50±33 (12–155) months, intervention) or had endoscopic removal (n=30, age: 53±30 (10–129) months, control)	Control: endoscopic removal (surgery)	significance level provided 80% power to detect differences in spontaneous-passage rates between the 2 groups of 10% vs 44% or 5% vs 36%.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Spontaneous coin passage (n)	Observation versus endoscopic removal	Not statistically significant: 7/30 vs 9/30 §, RR:0.78, 95%CI [0.33;1.82]* ¥ (p=0.56)	1, 30 vs 30 (power-analysis)	Waltzman, 2005

* Calculations done by the reviewer(s) using Review Manager software
¥ Imprecision (large variability of results)
§ Imprecision (low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Waltzman, 2005	Randomized, allocation concealment unclear	Unclear	No	No	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Low number of events and large variability in results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Moderate [B]**	

Conclusion	There is limited evidence neither in favour of watchful waiting nor endoscopic removal. A statistically significant decreased spontaneous coin passage, when watchful waiting compared to endoscopic removal, could not be demonstrated (Waltzman 2005). Evidence is of moderate quality and results of this study are imprecise due to the low number of events and large variability of results.
Reference(s)	**Individual studies** Waltzman ML, Baskin M, Wypij D, Mooney D, Jones D, Fleisher G. *A randomized clinical trial of the management of esophageal coins in children*. Pediatrics. 2005 Sep;116(3):614-619.

Abdominal injury – Posture (First Aid)

Question (PICO)	In humans with abdominal injury (P), does a certain posture (I) compared to another posture (C) change functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "abdominal injuries"] OR "abdominal injur*":ti,ab,kw OR "abdominal wound*":ti,ab,kw OR abdominal trauma:ti,ab,kw 2. [mh Posture] OR posture:ti,ab,kw OR position:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "abdominal injuries"[Mesh] OR (abdominal[TIAB] AND (injur*[TIAB] OR wound*[TIAB] OR trauma[TIAB])) 2. Posture[Mesh] OR posture[TIAB] OR position[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'abdominal injury'/exp OR (abdominal NEXT/1 injur*):ab,ti OR (abdominal NEXT/1 wound*):ab,ti OR (abdominal NEXT/1 trauma):ab,ti 2. 'body posture'/exp OR posture:ab,ti OR 'body position':ab,ti 3. 1-2 AND
Search date	31 August 2015
In/Exclusion criteria	**Population**: Include: People with abdominal injury. Exclude: pregnant women. **Intervention**: certain posture **Comparison**: another posture **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Abdominal injury – Pressure (First Aid)

Question (PICO)	In humans with abdominal injury (P), is applying firm pressure (I) compared to not doing this (C) effective to prevent bulging of the intestines (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "abdominal injuries"] or (abdominal:ti,ab,kw AND (injur*:ti,ab,kw OR wound*:ti,ab,kw OR trauma:ti,ab,kw)) 2. evisceration:ti,ab,kw OR disembowelment:ti,ab,kw 3. #1 AND #2 **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "abdominal injuries"[Mesh] OR (abdominal[TIAB] AND (injur*[TIAB] OR wound*[TIAB] OR trauma[TIAB])) 2. evisceration[TIAB] OR disembowelment[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'abdominal injury'/exp OR (abdominal:ab,ti AND (injur*:ab,ti OR wound*:ab,ti OR trauma:ab,ti)) 2. 'evisceration'/exp OR evisceration:ab,ti OR disembowelment:ab,ti 3. 1-2 AND
Search date	31 August 2015
In/Exclusion criteria	**Population**: People with abdominal injury **Intervention**: Pressure on the wound **Comparison**: no pressure on the wound **Outcome**: evisceration of organs, disembowelment **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Abdominal injury (bulging organs) – Pushing organs back (First Aid)

Question (PICO)	In humans with bulging organs (P), does not pushing the organs back (I) compared to pushing the organs back (C) change functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "abdominal injuries"] or (abdominal:ti,ab,kw AND (injur*:ti,ab,kw OR wound*:ti,ab,kw OR trauma:ti,ab,kw)) 2. evisceration:ti,ab,kw OR disembowelment:ti,ab,kw 3. #1 AND #2 **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "abdominal injuries"[Mesh] OR (abdominal[TIAB] AND (injur*[TIAB] OR wound*[TIAB] OR trauma[TIAB])) 2. evisceration[TIAB] OR disembowelment[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'abdominal injury'/exp OR (abdominal:ab,ti AND (injur*:ab,ti OR wound*:ab,ti OR trauma:ab,ti)) 2. 'evisceration'/exp OR evisceration:ab,ti OR disembowelment:ab,ti 3. 1-2 AND
Search date	31 August 2015
In/Exclusion criteria	**Population**: People with abdominal injury and eviscerating organs or disembowelment. **Intervention**: Not pushing the organs back in the abdomen **Comparison**: Pushing the organs back in the abdomen **Outcome**: evisceration of organs, disembowelment **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Side stitches – Stop physical acticity (First Aid)

Question (PICO)	In humans (P), is stopping the physical activity (I), compared to continuing with physical activity (C), effective to reduce side stitches (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh sports] OR [mh exercise] OR sport*:ti,ab,kw OR exercise:ti,ab,kw 2. [mh "abdomen, acute"] OR Stitch*:ti,ab,kw OR "side ache":ti,ab,kw OR "side pain":ti,ab,kw OR "exercise-related transient abdominal pain":ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Sports[Mesh] OR exercise[TIAB] OR sport*[TIAB] OR exercise[TIAB] 2. "Abdomen, acute"[Mesh] OR stitch*[TIAB] OR "side ache"[TIAB] OR "side pain"[TIAB] OR "exercise-related transient abdominal pain"[TIAB] OR ETAP[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Sport/exp OR exercise/exp OR sport*:ab,ti OR exercise:ab,ti 2. 'acute abdomen'/exp OR stitch*:ab,ti OR 'side ache':ab,ti OR 'side pain':ab,ti OR 'exercise-related transient abdominal pain':ab,ti OR ETAP:ab,ti 3. 1-2 AND
Search date	20 August 2015
In/Exclusion criteria	**Population**: Healthy people who perform sports with side stitches **Intervention**: Stopping physical activity **Comparison**: Continuing physical activity **Outcome**: reduction of side stitches **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	Not applicable

Side stitches – Physical manoeuvres (First Aid)

Question (PICO)	In humans (P), are certain physical manoeuvres (I), compared to no physical manoeuvres (C), effective to reduce side stitches (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh sports] OR [mh exercise] OR sport*:ti,ab,kw OR exercise:ti,ab,kw 2. [mh "abdomen, acute"] OR Stitch*:ti,ab,kw OR "side ache":ti,ab,kw OR "side pain":ti,ab,kw OR "exercise-related transient abdominal pain":ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Sports[Mesh] OR exercise[TIAB] OR sport*[TIAB] OR exercise[TIAB] 2. "Abdomen, acute"[Mesh] OR stitch*[TIAB] OR "side ache"[TIAB] OR "side pain"[TIAB] OR "exercise-related transient abdominal pain"[TIAB] OR ETAP[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Sport/exp OR exercise/exp OR sport*:ab,ti OR exercise:ab,ti 2. 'acute abdomen'/exp OR stitch*:ab,ti OR 'side ache':ab,ti OR 'side pain':ab,ti OR 'exercise-related transient abdominal pain':ab,ti OR ETAP:ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	20 August 2015
In/Exclusion criteria	**Population**: Healthy people who perform sports with side stitches **Intervention**: Long exhalation, contraction or relaxation of abdominal muscles, increased impact of foot strike, modified breathing, tightened abdominal belt. **Comparison**: normal exhalation, no physical manoeuvres **Outcome**: reduction of side stitches **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomized controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available.

	Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison/Risk factor	Remarks
Plunkett, 1999, New Zealand	Experimental: randomized controlled trial (within subjects design)	7 subjects completed a single trial in which they ran once, for 15 min, 20 min after consuming a mass-adjusted volume of Coca Cola. The first 4 minutes of exercise was steady uninterrupted running, thereafter the subjects tested the effects of the 5 physical manoeuvres on the intensity of their stitch.	1. Contracted abdominal muscles: contract muscles, lean forward while running, and push in on the site of the pain 2. Increased impact of foot strike: land heavily on the treadmill with each step 3. Modified breathing: breathing at a higher functional residual capacity (more air in the lungs at the end of expiration); resist each expiration by breathing out through pursed lips 4. Relaxed abdominal muscles: loosen up or relax stomach or abdominal muscles 5. Tightened abdominal belt: weight belt around the waist with a small towel between their abdomen and the front of the belt. At the designated time, they tightened the belt as much as possible and tensed the abdominal musculature. [Only data at 60 s (before physical manoeuvre) and 80s (during physical manoeuvre) were extracted]	

Synthesis of findings

Outcome	Comparison/Risk factor	Effect Size	#studies, # participants	Reference
Intensity of stitch	Contracted abdominal muscles vs no manoeuvre	Statistically significant: 0.71±2.29 vs 3.14±5.14 λ MD: -2.43 £† (p=0.03-0.0001) *In favour of contracted abdominal muscles*	1, 7 vs 7 § (within subjects design)	Plunkett, 1999
	Increased impact of foot strike vs no manoeuvre	Not statistically significant: 2.71±5.29 vs 3.14±5.86 λ MD: -0.43 £† (p>0.05)		
	Modified breathing vs no manoeuvre	Statistically significant: 1.43±3.43 vs 2.86±4.00 λ MD: -1.43 £† (p=0.03-0.0001) *In favour of modified breathing*		

	Relaxed abdominal muscles vs no manoeuvre	Not statistically significant: 2.29±4.57 vs 2.86±4.86 λ MD: -0.57 £† (p>0.05)		
	Tightened abdominal belt vs no manoeuvre	Statistically significant: 0.71±1.86 vs 3.00±4.00 λ MD: -2.29 £† (p=0.03-0.0001) *In favour of tightened abdominal belt*		

Mean ± SD (unless otherwise indicated)
£ No CI available
† Imprecision (lack of data)
§ Imprecision (limited sample size)
λ Data extracted from graph

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Plunkett, 1999	unclear, Latin square randomization, but nothing mentioned on allocation concealment	Yes, but not possible	No	No, loss to follow-up is reported	within subjects design

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/low number of events/lack of data
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is limited evidence in favour of contracted abdominal muscles, modified breathing and tightened abdominal belt. It was shown that contracting the abdominal muscles, modifying your breathing or tightening an abdominal belt resulted in a statistically significant decrease of intensity of side stitches, compared to not doing these manoeuvres (Plunkett 1999). Evidence is of low quality and results cannot be considered precise due to limited sample size and lack of data. There is limited evidence neither in favour of relaxed abdominal muscles or increased impact of foot strike nor not doing this. A statistically significant decrease of intensity of side stitches, using increased impact of foot strike or relaxed abdominal muscles compared to no manoeuvre, could not be demonstrated (Plunkett 1999). Evidence is of low quality and results of this study are imprecise due to limited sample size and lack of data.
Reference(s)	**Individual studies** Plunkett BT, Hopkins WG. *Investigation of the side pain "stitch" induced by running after fluid ingestion*. Med Sci Sports Exerc 1999, 31(8):1169-1175

Side stitches – Drinking (Prevention)

Question (PICO)	In humans (P), is drinking before sporting (I), compared to not drinking before sporting (C), effective to prevent side stitches (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh sports] OR [mh exercise] OR sport*:ti,ab,kw OR exercise:ti,ab,kw 2. [mh "abdomen, acute"] OR Stitch*:ti,ab,kw OR "side ache":ti,ab,kw OR "side pain":ti,ab,kw OR "exercise-related transient abdominal pain":ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Sports[Mesh] OR exercise[TIAB] OR sport*[TIAB] OR exercise[TIAB] 2. "Abdomen, acute"[Mesh] OR stitch*[TIAB] OR "side ache"[TIAB] OR "side pain"[TIAB] OR "exercise-related transient abdominal pain"[TIAB] OR ETAP[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Sport/exp OR exercise/exp OR sport*:ab,ti OR exercise:ab,ti 2. 'acute abdomen'/exp OR stitch*:ab,ti OR 'side ache':ab,ti OR 'side pain':ab,ti OR 'exercise-related transient abdominal pain':ab,ti OR ETAP:ab,ti 3. 1-2 AND Guidelines, systematic reviews, retrieved with the above searches, and used as source for individual studies: Pauwels, 2012 Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	24 August 2015
In/Exclusion criteria	**Population**: Healthy people who perform sports **Intervention**: Drinking fluids before sporting **Comparison**: not drinking fluids before sporting **Outcome**: side stitches **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Plunkett, 1999, New Zealand	Experimental: randomized controlled trial (within subjects design)	10 volunteers, mean age 21±2 yr, height 180±5 cm and weight 81±8 kg. They were active participants in several sports, non was a competitive runner.	1. Water 2. Decarbonated Coca-Cola 3. Exceed: commercially available energy drink 4. Duphalac (lactulose solution): a pharmaceutical preparation for the treatment of constipation 5. No fluids [data from Duphalac were not extracted] The volume consumed was 14 ml/kg of body mass	Subjects were tested at 11:00 h each day, with several days or rest between trials. After warm-up, subjects consumed the given fluid as quickly as possible and then immediately began running on the treadmill. They ran 5 bouts of 5 minutes with 10 minutes of rest between bouts.
Morton, 2004, Australia	Experimental: randomized controlled trial (within subjects design)	40 subjects (30 males, 10 females), mean age 21.0±0.5 yrs, height 177.1±1.4 cm, weight 71.9±1.9 kg, who claimed to be susceptible to ETAP. All subjects were active and considered themselves to be in good physical condition. Each subject performed four trials that involved running on a treadmill for 23 min at a velocity selected by the subjects as their recreational running speed.	1. Flavoured water: no carbohydrate, osmolality = 48 mosmol/L, pH 3.3 2. Sports drink: freshly mixed Gatorade®, 6% total carbohydrate, 295 mosmol/L, pH 3.3 3. Reconstituted fruit juice: BERRI®, Valencia Orange, 10.4% total carbohydrate, 489 mosmol/L, pH 3.2 20 min prior to treadmill exercise, subjects consumed 6 ml/kg body mass of the fluid, and then a further 4 ml/kg 10 min prior to commencement of exercise. Immediately prior to exercise, the subjects then consumed 2 ml/kg body mass and this volume was continued every 4 min throughout the trial. In total, the subjects consumed 22 ml/kg body mass of fluid during the 43-min testing session.	ETAP = exercise-related transient abdominal pain The four testing sessions were separated by approximately 1 week in order to minimize the possibility of a carryover effect.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Intensity of stitch	Water vs no fluid	First bout: Statistically significant:	1, 10 vs 10 § (within subjects design)	Plunkett, 1999

		1.47±3.47 vs 0.21±0.95 λ MD: 1.26 £† (p<0.0001) *In favour of no fluid*		
		Fourth bout: Statistically significant: 1.79±3.89 vs 0.53±1.47 λ MD: 1.26 £† (p=0.003-0.02) *In favour of no fluid*		
		Fifth bout: Statistically significant: 1.79±3.05 vs 0.21±0.74 λ MD: 1.58 £† (p=0.003-0.02) *In favour of no fluid*		
	Exceed vs no fluid	First bout: Statistically significant: 1.47±3.16 vs 0.21±0.95 λ MD: 1.26 £† (p<0.0001) *In favour of no fluid*		
		Fourth bout: Not statistically significant: 0.63±1.89 vs 0.53±1.47 λ MD: 0.10 £† (p=0.6)		
		Fifth bout: Not statistically significant: 0.63±2.11 vs 0.21±0.74 λ MD: 0.42 £† (p=0.9)		
	decarbonated Coca-Cola vs no fluid	First bout: Statistically significant: 1.68±3.16 vs 0.21±0.95 λ MD: 1.47 £† (p<0.0001) *In favour of no fluid*		
		Fourth bout: Statistically significant: 2.21±3.89 vs 0.53±1.47 λ MD: 1.68 £† (p=0.003-0.02) *In favour of no fluid*		
		Fifth bout: Statistically significant: 1.89±3.16 vs 0.21±0.74 λ MD: 1.68 £† (p=0.003-0.02) *In favour of no fluid*		
ETAP mean severity (mean±SE)	Flavored water vs no fluid	Not statistically significant: 0.6±0.1 vs 0.4±0.1 MD: 0.2 £† (p>0.05)	1, 40 vs 40 § (within subjects design)	Morton, 2004
	Sport drink vs no fluid	Not statistically significant: 0.8±0.2 vs 0.4±0.1 MD: 0.4 £†		

		(p>0.05)		
	Fruit juice vs no fluid	Statistically significant: 1.3±0.2 vs 0.4±0.1 MD: 0.9 £† (p<0.05) *In favour of no fluid*	1, 38 vs 40 § (within subjects design)	
Incidence of ETAP	Flavoured water vs no fluid	Statistically significant: 28/40 vs 16/40 § OR: 3.50 *£† (p<0.05) *In favour of no fluid*	1, 40 vs 40 (within subjects design)	
	Sport drink vs no fluid	Statistically significant: 28/40 vs 16/40 § OR: 3.50 *£† (p<0.05) *In favour of no fluid*		
	Fruit juice vs no fluid	Statistically significant: 32/40 vs 16/40 § OR: 6.00 *£† (p<0.05) *In favour of no fluid*	1, 38 vs 40 (within subjects design)	
Duration of ETAP (min, mean±SE)	Flavoured water vs no fluid	Not statistically significant: 9.8±1.2 vs 6.8±0.7 MD: 3.0 £† (p>0.05)	1, 40 vs 40 § (within subjects design)	
	Sport drink vs no fluid	Statistically significant: 13.2±1.4 vs 6.8±0.7 MD: 6.4 £† (p<0.05) *In favour of no fluid*		
	Fruit juice vs no fluid	Statistically significant: 14.4±1.0 vs 6.8±0.7 MD: 7.6 £† (p<0.05) *In favour of no fluid*	1, 38 vs 40 § (within subjects design)	

Mean ± SD (unless otherwise indicated)
* Calculations done by the reviewer(s) using Review Manager software
£ No CI available
† Imprecision (lack of data)
§ Imprecision (limited sample size or low number of events)
λ Data extracted from graph

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Plunkett, 1999	unclear, Latin square randomization, but nothing mentioned on allocation concealment	Yes, but not possible	No	No, loss to follow-up is reported	within subjects design
Morton, 2004	unclear, Latin square randomization, but nothing	Yes, but not possible	No	No, loss to follow-up is reported	within subjects design

	mentioned on allocation concealment				

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/low number of events/lack of data
Inconsistency	0	
Indirectness	0	
Publication bias	-1	Study of Morton was financed by a grant provided by Gatorade, which was one of the test solutions
QUALITY (GRADE)	**Final grading Very low [C]**	

Conclusion	There is limited evidence in favour of no fluid ingestion. In making this evidence conclusion, we take into account that the majority of the outcomes are statistically significant. It was shown that drinking fluids before exercise resulted in a statistically significant increase of incidence, duration and severity of side stitches, compared to not drinking fluids before exercise (Plunkett 1999, Morton 2004). Evidence is of very low quality and results cannot be considered precise due to limited sample size or low number of events and lack of data. A statistically significant decrease of intensity of stitch after 20-25 min of running, using Exceed sport drink compared to no fluid, could not be demonstrated (Plunkett 1999). A statistically significant decrease of ETAP severity, using sport drink or flavoured water compared to no fluid, could not be demonstrated (Morton 2004). A statistically significant decrease of duration of ETAP, using flavoured water compared to no fluid, could not be demonstrated (Morton 2004). Evidence is of very low quality and results of these studies cannot be considered precise due to limited sample size or low number of events and lack of data.
Reference(s)	**Individual studies** Plunkett BT, Hopkins WG. *Investigation of the side pain "stitch" induced by running after fluid ingestion*. Med Sci Sports Exerc 1999, 31(8):1169-1175 Morton DP, Aragón-Vargas LF, Callister R. *Effect of ingested fluid composition on exercise-related transient abdominal pain*. Int J Sport Nutr Exerc Metab 2004, 14:197-208 **Systematic reviews** Pauwels N, De Buck E. *BestBET 1: Is Exercise-related transient abdominal pain (stitch) while running preventable?* Emerg Med J 2012, 29:930-931

Back pain – Heat or cold application (First Aid)

Question (PICO)	In humans with back pain (P), is applying heat or cold (I) vs not doing this (C) effective to reduce symptoms of pain (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "back pain"] OR (back NEXT pain):ti,ab,kw OR backache:ti,ab,kw 2. Heat:ti,ab,kw OR hot:ti,ab,kw OR warm:ti,ab,kw OR cold:ti,ab,kw OR ice:ti,ab,kw 3. 1-2 AND

	MEDLINE (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Back pain"[Mesh] OR "Back pain"[TIAB] OR "backache"[TIAB] 2. Heat[TIAB] OR hot[TIAB] OR warm[TIAB] OR cold[TIAB] OR ice[Mesh 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'backache'/exp OR 'back pain':ab,ti OR 'backache':ab,ti 2. Heat:ab,ti OR hot:ab,ti OR warm:ab,ti OR cold:ab,ti OR ice:exp 3. 1-2 AND Guidelines, systematic reviews, retrieved with the above searches, and used as source for individual studies: French, 2006 (update expected end of 2015) Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	9 March 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Mayer, 2005, USA	Experimental: randomized controlled trial	100 participants (29 male, 71 female), mean age 31.2 years, with acute (less than 3 months) low back pain. Heat wrap (n=25) vs	1. Heat wrap alone: disposable ThermaCare Heat Wrap applied to lumbar area, 40°C for 8 hours/day for 5 consecutive days 2. McKenzie exercise alone	Studies were cited in Cochrane systematic review French 2006

		McKenzie exercise (n=25) vs Heat wrap + McKenzie exercise (n=24) vs educational booklet (n=26)	3. Heat wrap + McKenzie exercise 4. Educational booklet: participants were advised to closely follow the recommendations, except that they were asked to refrain from performing specific exercises for the low back, using heat or cold modalities, and receiving spinal manipulation.	
Nadler, 2003a, USA	Experimental: randomized controlled trial	219 participants (100 male, 119 female), mean age 36.1 years, with acute (less than 3 months) non-specific low-back pain. Heat wrap (n=95) vs oral placebo (n=96) vs oral ibuprofen (n=12) vs unheated wrap (n=16)	1. Heat wrap (ThermaCare Heat Wrap), 40°C, worn for approximately 8 hrs/day. 2. Oral placebo: 2 tablets 3x/day, spaced 6 h apart 3. Oral ibuprofen: 200 mg, 2 tablets, 3x/day, spaced 6 h apart 4. Unheated wrap [data on ibuprofen were not extracted]	
Nadler, 2003b, USA	Experimental: randomized controlled trial	76 participants (27 male, 49 female), mean age 41.4 years, with acute (less than 3 months) non-specific low-back pain. Heat wrap (n=33) vs oral placebo (n=34) vs oral ibuprofen (n=4) vs unheated wrap (n=5)	1. Heat wrap: ThermaCare Heat Wrap, 40°C, applied ±15-20 min before participants retired to bed and worn during sleep for ±8 h each night for 3 consecutive nights 2. Oral placebo: 2 tablets, administered ±15-20 min before patients retired to bed each night, for 3 consecutive nights 3. Oral ibuprofen: 2 tablets, total dose 400 mg, administered ±15-20 min before patients retired to bed each night, for 3 consecutive nights 4. Unheated wrap: applied ±15-20 min before participants retired to bed and worn during sleep for ±8h each night for 3 consecutive nights [data on ibuprofen were not extracted]	
Nuhr, 2004, Austria	Experimental: Randomized controlled trial	90 participants (57 male, 33 female), mean age 36.8±8.2 years, with first episode acute (<6 hrs) low-back pain. Resistive heating (n=47) vs passive warming (n=43)	1. Resistive heating: 42°C via a carbon-fibre electric heating blanket, which was in turn covered by a single woollen blanket. Mean duration of treatment: 24.8±8.1 min. 2. Passive warming: Participant covered with same carbon-fibre electric heating blanket, which was in turn covered by single woollen blanket. Heating of electric blanket was not activated. Mean duration of treatment: 26.2±9.3 min.	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Pain relief	Heat + exercise vs exercise alone	Day 2: Not statistically significant: 1.5±1.47 vs 1±1 MD: 0.50, 95%CI [-0.21, 1.21], (p=0.17) ¥ Day 4: Not statistically significant: 2.5±1.47 vs 1.7±1.5 MD: 0.80, 95%CI [-0.03, 1.63], (p=0.059) ¥ Day 7: Statistically significant: 3.4±0.98 vs 2±1.5 MD: 1.40, 95%CI [0.69, 2.11], (p=0.00010) *In favour of heat+exercise*	1, 24 vs 25 §	Mayer, 2005
Pain relief	Heat vs placebo	Statistically significant: MD: 1.06, 95%CI [0.68; 1.45], (p<0.00001) *In favour of heat*	2, 128 vs 130 §	Nadler 2003a, Nadler 2003b
	Heat vs educational booklet	Day 2: Statistically significant: 1.4±1 vs 0.8±1.02 MD: 0.60, 95%CI [0.05, 1.15], (p=0.034) *In favour of heat* Day 4: Statistically significant: 2±1 vs 0.9±1.02 MD: 1.10, 95%CI [0.55, 1.65], (p=0.00010) *In favour of heat* Day 7: Statistically significant: 2.3±2 vs 1.4±1.53 MD: 0.90, 95%CI [-0.08, 1.88], (p=0.072) *In favour of heat*	1, 25 vs 26 §	Mayer 2005
Pain (VAS)	Electric blanket vs non-heated blanket	Statistically significant: MD: -32.20, 95%CI [-38.69, -25.71], (p<0.00001) *In favour of heat*	1, 47 vs 43 §	Nuhr 2004
Pain affect	Heat vs placebo	Statistically significant: MD: -13.50, 95%CI [-21.27, -5.73], (p=0.00066) *In favour of heat*	1, 33 vs 34 §	Nadler, 2003b
Function change scores (Roland-Morris Disability Questionnaire)	Heat + exercise vs exercise alone	Day 2: Not statistically significant: 0.4±2.45 vs -0.2±2.5 MD: 0.60, 95%CI [-0.79, 1.99], (p=0.40) ¥	1, 24 vs 25 §	Mayer, 2005

		Day 4: Not statistically significant: -2.5±3.43 vs -1.3±3.5 MD: -1.20, 95%CI [-3.14, 0.74], (p=0.23) ¥ Day 7: <u>Statistically significant:</u> -5.5±3.92 vs -2.3±4.0 MD: -3.20, 95%CI [-5.42, -0.98], (p=0.0047) *In favour of heat+exercise*		
	Heat vs educational booklet	Day 2: <u>Statistically significant</u>: -0.9±2.5 vs 0.5±2.55 MD: -1.40, 95%CI [-2.79, -0.01], (p=0.048) *In favour of heat* Day 4: <u>Statistically significant</u>: -2.2±3.5 vs 0.1±3.57 MD: -2.30, 95%CI [-4.24, -0.36], (p=0.020) *In favour of heat* Day 7: Not statistically significant: -2.8±4 vs -1.1±4.08 MD: -1.70, 95%CI [-3.92, 0.52], (p=0.13) ¥	1, 25 vs 26 §	
Function (MTAP = Multidimensional Task Ability Profile)	Heat + exercise vs exercise only	Day 2: Not statistically significant: 17.4±21.2 vs 16.1±20.5 MD: 1.30, 95%CI [-10.35, 12.95], (p=0.83) ¥ Day 4: <u>Statistically significant:</u> 43.8±26.9 vs 25.5±26.0 MD: 18.30, 95%CI 3.48, 33.12], (p=0.016) *In favour of heat+exercise* Day 7: <u>Statistically significant:</u> 68.7±31.4 vs 25.0±30.1 MD: 43.70, 95%CI [26.62, 60.78], (p<0.00001) *In favour of heat+exercise*	1, 24 vs 25 §	Mayer, 2005
Function	Heat vs placebo	<u>Statistically significant:</u> MD: -2.12, 95%CI [-3.07, -1.18], (p=0.000011) *In favour of heat*	2, 128 vs 130 §	Nadler 2003a, Nadler2003b

Mean ± SD (unless otherwise indicated)

¥ Imprecision (large variability of results)

§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Mayer, 2005	Unclear	Yes	No	Yes	
Nadler, 2003a	Unclear	Yes (patients + providers) No (outcome assessor)	No	No	
Nadler, 2003b	Unclear	Yes (patients + providers) No (outcome assessor)	No	No	
Nuhr, 2004	No	Yes (patients + providers) No (outcome assessor)	No	Yes	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence' and French 2006
Imprecision	-1	Limited sample sizes/ large variability of the results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	No evidence was found on cold application for back pain. There is limited evidence from 4 experimental studies in favour of heat. It was shown that heat+exercise resulted in a statistically significant increase of pain relief and function (MTAP) and a statistically significant decrease of function change scores (Roland-Morris Disability score), compared to exercise alone (Mayer 2005). It was shown that heat resulted in a statistically significant increase of pain relief and a statistically significant decrease of function change scores (Roland-Morris Disability score), pain and pain affect, compared to no heat (Mayer 2005, Nadler 2003a/b, Nuhr 2004). Evidence is of low quality and results cannot be considered precise due to limited sample size and/or large variability of results.
Reference(s)	**Articles** Mayer JM, Ralph L, Look M, Erasala GN, Verna JL, Matheson LN, Mooney V. *Treating acute low back pain with continuous low-level heat wrap therapy and/or exercise: a randomized controlled trial*. The Spine Journal 2005, 5(4): 395–403. Nadler SF, Steiner DJ, Erasala GN, Hengehold DA, Abeln SB, Weingand KW. *Continuous low-level heatwrap therapy for treating acute nonspecific low back pain*. Archives of physical medicine and rehabilitation 2003a, 84(3):329–334. Nadler SF, Steiner DJ, Petty SR, Erasala GN, Hengehold DA, Weingand KW. *Overnight use of continuous low-level heatwrap therapy for relief of low back pain*. Archives of physical medicine and rehabilitation 2003b, 8(3):335–42. Nuhr M, Hoerauf K, Bertalanffy A, Bertalanffy P, Frickey N, Gore C, Gustorff B, Kober A. *Active warming during emergency transport relieves acute low back pain*. Spine 2004, 29(14):1499–503. **Systematic reviews** French SD, Cameron M, Walker BF, Reggars JW, Esterman AJ. *Superficial heat or cold for low back pain*. Cochrane Database of Systematic Reviews 2006, Issue 1. Art No.:CD004750.

Back pain – Lift technique (Prevention)

Question (PICO)	In persons who have to lift heavy weight (P) is a certain lift technique (I) compared to another/no lift technique (C) better to prevent back problems (O)?
Search Strategy	Databases **GIN** (guidelines) using the search terms 'lift*' OR 'lumbago' OR 'back AND weight' OR 'back AND prevention' OR 'back AND heavy' **NGC** (guidelines) using the search terms 'lift*' OR 'lumbago' OR 'back pain AND prevention' OR 'back pain AND heavy' OR 'back injury' **BestBET** (best evidence topics) using the search terms: 'back' OR 'lift' OR 'lifting' OR 'lumbago' **The Cochrane Library** (systematic reviews) using the following search strategy: 1. MeSH descriptor: [Back pain] explode all trees 2. MeSH descriptor: [Back injury] explode all trees 3. #1 OR #2 **The Cochrane Library** (controlled trials) using the following search strategy: 1. MeSH descriptor: [Back pain] explode all trees 2. MeSH descriptor: [Back injury] explode all trees 3. #1 OR #2 4. lift* OR scoop* OR squat* 5. prevention 6. #4 OR #5 7. #3 AND #6 **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Back Pain/prevention and control"[Mesh] OR "Back Pain/etiology"[Mesh] OR "Back Injuries/prevention and control"[Mesh] OR "Back Injuries/etiology"[Mesh] OR "Back pain"[TIAB] 2. squat* [TIAB] OR stoop*[TIAB] OR bend* [TIAB] OR lift* [TIAB] OR Moving and lifting patients [Mesh] OR Weight lifting [Mesh] 3. 1 AND 2 **Embase** (via Embase.com interface) using the following search strategy: 1. 'backache'/exp 2. 'weight bearing'/exp OR 'weight lifting'/exp OR 'patient lifting'/exp OR squat*:ab:ti OR stoop*:ab,ti OR bend*:ab,ti OR lift*:ab,ti 3. 'risk factor'/exp OR 'prevention'/exp OR prevention:ab,ti 4. 1-3 AND Systematic reviews used as source for individual studies: Bigos, 2009 Linton, 2001 van Poppel, 2004 Verbeek, 2011 Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	01 February 2013
In/Exclusion criteria	**Population**: Include: populations with work-related risk of back pain for evaluating programs (e.g. nurses, baggage handlers and postal workers, as they are exposed to

	frequent manual lifting). Exclude: populations with work-related risk of back pain for determination of risk factors (not comparable to the risks of the relief service volunteers). **Intervention:** Include: studies focusing on individual designed programmes, programmes with feedback while working or programmes with more than a single training session. Exclude: studies about lumbar supports (back belts) and assistive devices. **Comparison:** Exclude: studies with comparison groups getting a training as well. **Outcome:** Include: all studies measuring back pain or back injuries as outcome. Exclude: studies measuring 'days off at work' or biomechanical outcomes (e.g. rotation of joints, pressure, spinal compression). **Study design**: Include: all experimental and observational study design defined in our methodological charter.

Characteristics of included studies

Author, year	Study design	Population	Comparison	Remarks
Kraus, 2002, USA	Experimental: Cluster-Randomized controlled trial	Workers from 9 home care agencies (n=12772)	Intervention: Information about low back health; Control: no information	
Redell, 1992, USA	Experimental: Randomized controlled trial	Fleet service clerks (n=642), with and without history of back pain	1h training programme on back injury prevention (video + demonstration of exercises and lifting techniques) vs No training	
Walsh ,1990, USA	Experimental: Randomized controlled trial	Warehouse workers (n=90)	1h training session in back pain prevention and body mechanics vs no training	
Mundt, 1993, USA	Observational: Case-control	Persons with herniated disc (287 cases, 359 controls)	Non-occupational lifting in different ways (knees bent/straight: back bent/straight)	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
TRAINING				
Number of persons with back injury	Lifting advice vs No advice	No statistically significant: 89/4300 vs 109/4635 OR: 0.88, 95%CI [0.66;1.16] (p=0.37) *§* The effect size was calculated by the reviewer(s) using the Review Manager Software	n=8935	Kraus 2002
Back injury rate	1h training programme vs No training	No statistically significant difference. Data lacking.	n=642	Redell 1992
Back injury rate	1h training programme vs no training	No statistically significant difference. Data lacking.	n=54 *	Walsh 1990
POSTURE				
Symptoms of herniated lumbar disk	1) Knees bent, back straight 2) Knees bent, back bent 3) Knees straight, back bent	Statistically significant: 1) RR: 0.58, 95%CI [0.36;0.92] *With beneficial effect for knees bent, back straight*	287 cases, 359 controls	Mundt 1993

		No statistically significant difference: 2) RR: 1.16, 95%CI [0.59;2.30] *§* <u>Statistically significant</u>: 3) RR: 2.25, 95%CI [1.08;4.70] *With harmful effect for knees straight, back bent*		
	4) Arm extension when lift started 5) Arm extension when lift ended 6)Twisted while lifting	Less than ½ the time No statistically significant 1) RR: 0.97, 95%CI [0.61;1.54] *§* 2) RR: 1.08, 95%CI [0.69;1.71] *§* 3) RR: 0.98, 95%CI [0.66;1.45] *§* More than ½ the time No statistically significant 1) RR = 1.17, 95% CI [0.74 ; 1.86] *§* 2) RR= 1.08, 95% CI [0.67 ; 1.74] *§* 3) RR = 1.35, 95% CI [0.74 ; 2.47] *§*		

§ Imprecision due to large variability of the results.

* Imprecision due to limited sample size.

*§Imprecision due to limited sample size and large variability of the results.

Training

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations	Remarks
Kraus, 2002	Unclear, not specified in the article	Unclear, not specified in the article	No	No	Cluster-randomization	
Redell, 1992	Unclear, not specified in the article	Unclear, not specified in the article	No	No	Randomized block design	
Walsh, 1990	Unclear, not specified in the article	No	No	No		

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Original data are lacking (outcome only mentioned in text); large variability of the results
Inconsistency	0	
Indirectness	0	
Publication bias	0	Not evaluated
QUALITY (GRADE)	**Final grading Low [C]**	

Posture

Quality of evidence

Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequately short follow-up	Other limitations	Remarks
Mundt, 1993	No	No	No	No		

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	0	
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is inconclusive evidence from 3 experimental studies on the effect of a **single training session** on back pain (*no evidence of effect*) (Kraus 2002, Redell 1992, Walsch 1990, C). In 3 experimental studies, a statistically significant effect of a single training session on back pain could not be demonstrated, due a to large variability of the results (Kraus 2002), lacking study data (Redell 1992, Walsch 1990) and a limited sample size (Walsch 1990). There is conclusive evidence from 1 observational study on the effect of **bending knees/back straight** on back pain (*evidence of effect*) (Mundt 1993, C). In 1 observational study it was shown that bending knees/back straight resulted in a statistically significant decrease in symptoms of herniated lumbar disk, compared to knees straight/bending back (Mundt 1993, C). There is inconclusive evidence from 1 observational study on the effect of **arm extension or twisting** while lifting on back pain (*no evidence of effect*) (Mundt 1993, C). In 1 observational study, a statistically significant effect of arm extension or twisting while lifting on back pain could not be demonstrated, due to a large variability of the results (Mundt 1993, C).
Reference(s)	**Articles** Kraus JF, Schaffer KB, Rice T, Maroosis J, Harper J. *A field trial of back belts to reduce the incidence of acute low back injuries in New York City home attendants*. Int J Occup Environ Health 2002, 8(2):97-104. Mundt DJ, Kelsey JL, Golden AL, Pastides H, Berg AT, Sklar J, Hosea T, Panjabi MM. *An Epidemiologic study of non-occupational lifting as a risk factor for herniated lumbar intervertebral Disc*. Spine (Phila Pa 1976). 1993, 18(5):595-602. Reddell CR, Congleton JJ, Dale Huchingson R, Montgomery JF. *An evaluation of a weightlifting belt and back injury prevention training class for airline baggage handlers.* Appl Ergon 1992, 23(5):319-29. Walsh NE, Schwartz RK. *The influence of prophylactic orthoses on abdominal strength and low back injury in the workplace.* Am J Phys Med Rehabil 1990, 69(5):245-250. **Systematic reviews** Bigos SJ, Holland J, Holland C, Webster JS, Battie M, Malmgren JA. *High-quality controlled trials on preventing episodes of back problems: systematic literature review in working-age adults.* Spine J 2009, 9(2):147-168. Linton SJ, van Tulder MW. *Preventive interventions for back and neck pain problems.* Spine (Phila Pa 1976) 2001, 26(7):778-87

	Martimo KP, Verbeek J, Karppinen J, Furlan AD, Takala EP, Kuijer PP, Jauhiainen M, Viikari-Juntura E. *Effect of training and lifting equipment for preventing back pain in lifting and handling: systematic review*. BMJ 2008, 336(7641):429-431 van Poppel MN, Hooftman WE, Koes BW. *An update of a systematic review of controlled clinical trials on the primary prevention of back pain at the workplace*. Occup Med (Lond) 2004, 54(5):345-352. Verbeek JH, Martimo KP, Karppinen J, Kuijer PP, Viikari-Juntura E, Takala EP. *Manual material handling advice and assistive devices for preventing and treating back pain in workers*. Cochrane Database Syst Rev. 2011

Back pain – sitting/standing/walking (Risk factor)

Question (PICO)	In humans (P), is a sitting, standing or walking (I) a risk factor for back pain (O)?
Search Strategy	Databases The following search strategies were used to search for systematic reviews: **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "back pain"] OR "back pain":ti,ab,kw OR backache:ti,ab,kw 2. [mh posture] OR posture:ti,ab,kw OR sitting:ti,ab,kw OR stand*:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for guidelines and systematic reviews using the following search strategy: 1. "Back pain"[Mesh] OR "back pain"[TIAB] OR backache[TIAB] 2. Posture[Mesh] OR posture[TIAB] OR sitting[TIAB] OR stand*[TIAB] 3. ((((((((((Meta-Analysis as Topic[Mesh])) OR ((meta analy*[TIAB]))) OR ((metaanaly*[TIAB]))) OR ((Meta-Analysis[Publication Type]))) OR ((systematic review*[TIAB] OR systematic overview*[TIAB]))) OR ((Review Literature as Topic[Mesh])))) OR ((cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB]))) OR ((reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB]))) OR ((((selection criteria[TIAB] OR data extraction[TIAB])) AND ((Review[PT])))))) NOT ((Comment[PT] OR Letter[PT] OR Editorial[PT] OR animal[Mesh] NOT (animal[Mesh] AND human[Mesh]))) 4. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Backache/exp OR 'back pain':ab,ti OR backache:ab,ti 2. 'body position'/exp OR posture:ab,ti OR sitting:ab,ti OR stand*:ab,ti 3. 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti 4. 1-2 AND The following search strategies were used to search for studies on risk factors: The **Cochrane Library** using the following search strategy: 1. [mh "back pain"] OR "back pain":ti,ab,kw OR backache:ti,ab,kw 2. [mh "Risk factors"] OR (risk NEXT factor*):ti,ab,kw 3. 1-2 AND

	MEDLINE (via PubMed interface) for systematic reviews using the following search strategy: 1. "Back pain"[Mesh] OR "back pain"[TIAB] OR backache[TIAB] 2. Posture[Mesh] OR posture[TIAB] OR sitting[TIAB] OR stand*[TIAB] 3. "Risk factors"[Mesh] OR risk factor*[TIAB] 4. Epidemiologic Studies"[Mesh] OR "case-control"[TIAB] OR ((case[TIAB] OR cases[TIAB]) AND (control[TIAB] OR controls[TIAB])) OR "cohort study"[TIAB] OR "cohort analysis"[TIAB] OR "follow-up study"[TIAB] OR "observational study"[TIAB] OR "longitudinal"[TIAB] OR "retrospective"[TIAB] 5. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Backache/exp OR 'back pain':ab,ti OR backache:ab,ti 2. 'body position'/exp OR posture:ab,ti OR sitting:ab,ti OR stand*:ab,ti 3. 'risk factor'/exp OR (risk NEXT/1 factor*):ab,ti 4. 'cohort analysis'/exp OR 'case-control':ab:ti OR ((case:ab:ti OR cases:ab:ti) AND (control:ab:ti OR controls:ab:ti)) OR 'cohort study':ab:ti OR 'cohort analysis':ab:ti OR 'follow-up study':ab:ti OR 'observational study':ab:ti OR 'longitudinal':ab:ti OR 'retrospective':ab:ti 5. 1-4 AND Guidelines, systematic reviews, retrieved with the above searches, and used as source for individual studies: Chen, 2009 Roffey, 2010a Roffey, 2010b Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in MEDLINE (via PubMed interface).
Search date	31 August 2015
In/Exclusion criteria	**Population**: Include: Healthy adults. Exclude: pregnant women. **Risk factor**: Include: standing, sitting, walking. Exclude: shoe insoles, lumbar supports such as back belts, dynamic sitting, demographic or psychosocial risk factors, physical loading. **Comparison**: Include: not standing, not sitting, not walking. Exclude: comparison of standing/walking vs sitting. **Outcome**: Include: back pain. **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Cohort studies should include baseline and follow-up measurements. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Risk factor	Remarks
Andersen, 2007, Denmark	Observational: cohort study	1513 workers from 39 different work places (19 in service sector, 20 in different kinds of industry) who were free of severe pain at baseline and completed the follow-up after 24 months.	Several risk factors of which only the following were extracted: 1. Sitting > 30 minutes per hour vs not sitting > 30 minutes per hour 2. Standing > 30 minutes per hour vs not standing > 30 minutes per hour	
Croft, 1999, UK	Observational: cohort study	2715 adults (aged 18-75 years) from the South Manchester Back Pain Study who were free of recent low back pain at baseline. Follow-up at 12 months.	Several risk factors of which only the following was extracted: Walking <30 min per day vs walking >30 min per day	
Harkness, 2003, UK	Observational: cohort study	625 newly employed workers from 12 diverse occupational groups (police and army officers, supermarket and postal distribution centre, nurses, dentists and podiatry students). Participants who were pain free at baseline were followed-up after 1 year. Those who were still pain free at that point (n=501) were followed for another year.	Several risk factors of which only the following were extracted: 1. Sitting <2 h or ≥2 h vs no sitting 2. Standing <15 min, 15 min - <2 h, ≥ 2h vs no standing	Sample size was determined: 1000 subjects were required to have 80% power of detecting a doubling of risk associated with such a factor.
Macfarlane, 1997, UK	Observational: cohort study	784 individuals (aged 18-75 years) from the South Manchester Back Pain Study who were free of recent low back pain at baseline. Follow-up at 12 months.	Several risk factors of which only the following were extracted: 1. Sitting > 2 hr vs no sitting > 2 hr 2. Standing/walking > 2 hr vs no standing/walking > 2 hr	
Yip, 2004, China	Observational: cohort study	144 nurses from 6 Hong Kong district hospitals. Twelve months after a baseline interview and physical measurements, participants were questioned by telephone about the occurrence of LBP during the intervening period.	1. Standing < 2 hrs vs standing ≥4 hrs 2. Sitting < 2 hrs vs sitting ≥ 2 hrs 3. Walking 4 hours vs walking > 4 hours	Power calculation was based on the assumption that 33% of nurses with new LBP frequently bend to lift an item from floor level. The power of

				the study is 66% for 144 recruited nurses.

Synthesis of findings

Outcome	Risk factor	Effect Size	#studies, # participants	Reference
Sitting				
Low back pain	Sitting > 30 minutes per hour vs not sitting > 30 minutes per hour	Not statistically significant: HR: 0.9, 95%CI [0.6; 1.4] ¥ (p>0.05) £	1, 286 vs 1084	Andersen, 2007
	Sitting < 2 h vs no sitting	Not statistically significant: 47/243 vs 57/322 § aOR: 1.0, 95%CI [0.6; 1.7] ¥ (p>0.05)	1, 243 vs 322 (power analysis)	Harkness, 2003
	Sitting ≥ 2 h vs no sitting	Not statistically significant: 94/471 vs 57/322 § aOR: 1.0, 95%CI [0.6; 1.7] ¥ (p>0.05)	1, 471 vs 322	
	Sitting > 2 h vs no sitting > 2 h	Not statistically significant: Males: 24/115 vs 25/111 § OR: 0.9, 95%CI [0.1; 1.5] ¥ (p>0.05) <u>Statistically significant</u>: Females: 26/126 vs 44/116 § OR: 0.4, 95%CI [0.2; 0.7] (p<0.05) *With benefit for sitting > 2 h*	1, 115 vs 111 1, 126 vs 116	Macfarlane, 1997
	Sitting < 2 hrs vs sitting ≥ 2 hrs	Not statistically significant: 39/93 vs 17/51 § (p=0.47) ££†	1, 93 vs 51	Yip, 2004
Standing				
Low back pain	Standing > 30 minutes per hour vs not standing > 30 minutes per hour	<u>Statistically significant</u>: HR: 2.1, 95%CI [1.3; 3.3] (p<0.05) £ *With harm for standing > 30 minutes per hour*	1, 114 vs 1384	Andersen, 2007
	Standing < 15 min vs no standing	Not statistically significant: 53/328 vs 18/94 § aOR: 1.0, 95%CI [0.5; 1.9] ¥ (p>0.05)	1, 328 vs 94 (power analysis)	Harkness, 2003
	Standing 15 min - < 2 h vs no standing	Not statistically significant: 69/323 vs 18/94 § aOR: 1.4, 95%CI [0.7; 2.7] ¥ (p>0.05)	1, 323 vs 94 (power analysis)	
	Standing ≥ 2 h vs no standing	Not statistically significant: 58/292 vs 18/94 § aOR: 1.5, 95%CI [0.8; 3.0] ¥ (p>0.05)	1, 292 vs 94 (power analysis)	
	Standing < 2 hrs vs standing ≥4 hrs	Not statistically significant: 21/44 vs 35/100 § (p=0.19) ££†	1, 44 vs 100	Yip, 2004

Walking				
Low back pain	Walking < 30 min per day vs walking > 30 min per day	Not statistically significant: Males: RR: 1.0, 95%CI [0.8; 1.3] ¥ (p>0.05) £ Females: RR: 1.1, 95%CI [0.9; 1.4] ¥ (p>0.05) £	1, 125 vs 121 § 1, 152 vs 193 §	Croft, 1999
	Walking 4 hours vs walking > 4 hours	Not statistically significant: 36/102 vs 20/42 (p=0.37) ££†	1, 102 vs 42	Yip, 2004
Standing/walking				
Low back pain	Standing/walking >2 hr vs no standing/walking >2 hr	Not statistically significant: Males: 37/158 vs 12/68 § OR: 1.6, 95%CI [0.8; 3.3] ¥ (p>0.05) <u>Statistically significant</u>: Females: 54/148 vs 16/94 § OR: 2.9, 95%CI [1.5; 5.5] (p<0.05) *With harm for standing/walking > 2 hr*	1, 158 vs 68 1, 148 vs 94	Macfarlane, 1997

£ No raw data available
†† No effect size and CI available
¥ Imprecision (large variability of results)
† Imprecision (Lack of data)
§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations
Andersen, 2007	No	Unclear, possible recall bias	No, controlled for sex, age, occupational group and intervention group	No	
Croft, 1999	No	Unclear, possible recall bias for those who did not visit practitioner	No, adjusted for self-rated health and psychological distress, age	No	
Harkness, 2003	No	Yes, work exposures were assessed during last working day' and may not reflect a 'typical' working day	No, adjusted for those variables that were found to have an increased, decreased or significant association with new-onset LBP.	No	study of occupational cohort: 'healthy worker effect'

Macfarlane, 1997	No	Unclear, possible recall bias for those who did not visit practitioner	No	No	'healthy worker effect'
Yip, 2004	No	Unclear, possible recall bias	No	No	

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/low number of events/lack of data/large variability of the results
Inconsistency	0	
Indirectness	-1	Studies in occupational settings
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Conclusion	**<u>Sitting</u>** There is limited evidence neither for the benefit/harm of sitting a longer period compared to a shorter period or no sitting. In making this evidence conclusion, we place higher value on studies that looked at the entire population (taking into account sex as a confounding factor in their statistical analysis) instead of studies making a distinction between males and females. A statistically significant increased risk of low back pain in case of sitting > 30 min or 2 hours compared to sitting < 30 min or 2 hours could not be demonstrated (Andersen 2007, Harkness 2003, Macfarlane 1997). However, in one study it was shown that sitting >2 hours resulted in a statistically significant decreased risk of low back pain in females, compared to sitting < 2 hours (Macfarlane 1997). Evidence is of very low quality and results of these studies are imprecise due to low number of events, lack of data and/or large variability of results **<u>Standing</u>** There is limited evidence with harm for standing >30 minutes per hour. It was shown that standing >30 minutes per hour resulted in a statistically significant increased risk of low back pain, compared to not standing >30 minutes per hour (Andersen 2007). A statistically significant increased risk of low back pain in case of standing >2 or 4 hours compared to not standing >2 or 4 hours could not be demonstrated (Harkness 2003, Yip 2004). Evidence is of very low quality and results of these studies are imprecise due to low number of events, lack of data and/or large variability of results. **<u>Walking</u>** There is limited evidence neither for the benefit/harm of walking nor not walking. A statistically significant increased risk of low back pain in case of walking <30 minutes per day or walking 4 hours compared to walking >30 minutes per day or walking >4 hours could not be demonstrated (Croft 1999, Yip 2004). Evidence is of very low quality and results of these studies are imprecise due to low number of events, lack of data and/or large variability of results. **<u>Standing/walking combined</u>** There is limited evidence with harm for standing/walking >2 hours in females. It was shown that standing/walking >2 hours resulted in a statistically significant increased risk of low back pain, compared to not standing/walking >2 hours (Macfarlane 1997).

	However, a statistically significant increased risk of low back pain in case of standing/walking >2 hours compared to not standing/walking >2 hours could not be demonstrated in males (Macfarlane 1997). Evidence is of very low quality and results cannot be considered precise due to low number of events and/or large variability of results.
Reference(s)	**Individual studies** Andersen JH, Haahr JP, Frost P. *Risk factors for more severe regional musculoskeletal symptoms*. Arthritis & Rheumatism 2007, 56(4):1355-1364 Croft PR, Papageorgiou AC, Thomas E, Macfarlane GJ, Silman AJ. *Short-term physical risk factors for new episodes of low back pain. Prospective evidence from the South Manchester Back Pain Study*. Spine 1999, 24(15):1556-1561 Harkness EF, Macfarlane GJ, Nahit ES, Silman AJ, McBeth J. *Risk factors for new-onset low back pain amongst cohorts of newly employed workers*. Rheumatology 2003, 42:959-968. Macfarlane GJ, Thomas E, Papageorgiou AC, Croft PR, Jayson MIV, Silman AJ. *Employment and physical work activities as predictors of future low back pain*. Spine 1997, 22(10):1143-1149 Yip VYB. *New low back pain in nurses: work activities, work stress and sedentary lifestyle.* J Adv Nurs 2004, 46(4):430-440 **Systematic reviews** Chen S-M, Liu M-F, Cook J, Bass S, Lo SK. *Sedentary lifestyle as a risk factor for low back pain: a systematic review*. Int Arch Occup Environ Health 2009, 82:797-806 Roffey DM, Wai EK, Bishop P, Kwon BK, Dagenais S. *Casual assessment of occupational sitting and low back pain: results of a systematic review*. The Spine Journal 2010a, 10:252-261 Roffey DM, Wai EK, Bishop P, Kwon BK, Dagenais S. *Casual assessment of occupational standing or walking and low back pain: results of a systemtic review.* The Spine Journal, 10:262-272

Genital injury – Breathing patterns (First Aid)

Question (PICO)	In humans with a genital injury (P), is a certain way of breathing (I) compared to another way of breathing (C) effective to change functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh Genitalia] OR genital*:ti,ab,kw 2. [mh "wounds and injuries"] OR injur*:ti,ab,kw 3. [mh Respiration] OR breath*:ti,ab,kw OR inhal*:ti,ab,kw 4. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Genitalia[Mesh] OR genital*[TIAB] 2. "wounds and injuries"[Mesh] OR injur*[TIAB] 3. Respiration[Mesh] OR breath*[TIAB] OR inhal*[TIAB] 4. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'genital injury'/exp OR (('Genital system'/exp OR genital*:ab,ti) AND (injury:ab,ti OR injuries:ab,ti)) 2. Breathing/exp OR breath*:ab,ti OR inhal*:ab,ti 3. 1-2 AND

Search date	19 August 2015
In/Exclusion criteria	**Population**: Include: People with genital injuries **Intervention**: Include: certain ways of breathing **Outcome:** Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Genital injury – Cooling (First Aid)

Question (PICO)	In humans with a genital injury (P), is cooling (I) compared to no cooling (C) effective to change functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh Genitalia] OR genital*:ti,ab,kw 2. [mh "wounds and injuries"] OR injur*:ti,ab,kw 3. [mh Ice] OR [mh cryotherapy] OR Ice:ti,ab,kw OR cryotherapy:ti,ab,kw OR "cold therapy":ti,ab,kw 4. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Genitalia[Mesh] OR genital*[TIAB] 2. "wounds and injuries"[Mesh] OR injur*[TIAB]

	3. Ice[Mesh] OR cryotherapy[Mesh:NoExp] OR Ice[TIAB] OR cryotherapy[TIAB] OR cold therapy[TIAB] 4. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'genital injury'/exp OR (('Genital system'/exp OR genital*:ab,ti) AND (injury:ab,ti OR injuries:ab,ti)) 2. 'ice'/exp OR 'cryotherapy'/exp OR ice:ab,ti OR cryotherapy:ab,ti OR 'cold therapy':ab,ti 3. 1-2 AND
Search date	19 August 2015
In/Exclusion criteria	**Population**: Include: People with genital injuries **Intervention**: Include: cooling **Comparison**: Include: no cooling **Outcome:** Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Genital injury – Urinate (First Aid)

Question (PICO)	In humans with a genital injury (P), is urinating (I) compared to not urinating (C) effective to change functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy:

	1. [mh Genitalia] OR genital*:ti,ab,kw 2. [mh "wounds and injuries"] OR injur*:ti,ab,kw 3. [mh Urination] OR urinat*:ti,ab,kw OR micturition:ti,ab,kw 4. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Genitalia[Mesh] OR genital*[TIAB] 2. "wounds and injuries"[Mesh] OR injur*[TIAB] 3. Urination[Mesh] OR urinat*[TIAB] OR micturition[TIAB] 4. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'genital injury'/exp OR (('Genital system'/exp OR genital*:ab,ti) AND (injury:ab,ti OR injuries:ab,ti)) 2. micturition/exp OR urinat*:ab,ti OR micturition:ab,ti 3. 1-2 AND
Search date	19 August 2015
In/Exclusion criteria	**Population**: Include: People with genital injuries **Intervention**: Include: urination **Comparison**: Include: no urination **Outcome:** Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

LIMBS

Friction blisters – Deroofing or aspiration (First Aid)

Question (PICO)	Among people with a friction blister (P) is deroofing or aspiration (I) compared to leaving the blisters intact (C) effective to change tissue healing, functional recovery, pain, complications, time to resumption of usual activities, restoration to the pre-exposure condition, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. friction:ti,ab,kw OR pressure:ti,ab,kw 2. [mh "blister"] OR blister:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for systematic reviews, experimental and observational studies using the following search strategy: 1. "friction"[TIAB] OR "pressure"[TIAB] 2. "blister"[TIAB] OR "blisters"[TIAB] OR "blister"[Mesh] 3. 1-2 AND **Embase** (via Embase.com interface) for systematic reviews, experimental and observational studies using the following search strategy: 1. 'friction':ab:ti OR 'pressure':ab:ti 2. 'blister'/exp 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in MEDLINE (via PubMed interface).
Search date	09 March 2015
In/Exclusion criteria	**General project-related eligibility criteria:** **Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available.

	Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Swain 1987, UK	Experimental: non-randomized controlled trial	202 patients with 316 minor burns. Only thermal burns of the arms and legs that could be treated with paraffin gauze dressings were included.	Aspiration after 1 day vs. deroofing after 1 day vs. keeping blister intact for 10 days	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Number of blisters colonised with bacteria	Deroofing vs. keeping blister intact	Statistically significant: 78/102 vs 15/110 RR: 5.61, 95%CI [3.46; 9.08] (p<0.00001) * *In favour of keeping intact*	1, 102 vs. 110 blisters §	Swain, 1987
Number of blisters colonised with *Staphylococcus aureus*		Statistically significant: 45/102 vs 2/110 RR:24.26, 95%CI [6.04; 97.47] (p<0.00001) * *In favour of keeping intact*		
Number of blisters colonised with bacteria	Aspiration vs. keeping blister intact	Statistically significant: 73/104 vs 15/110 RR:5.15, 95%CI [3.16; 8.37] (p<0.00001) * *In favour of keeping intact*	1, 104 vs 110 blisters §	
Number of blisters colonised with *Staphylococcus aureus*		Statistically significant: 19/104 vs 2/110 RR:10.05, 95%CI [2.40; 42.08] (p=0.004) * *In favour of keeping intact*		

* The effect size and p-value was calculated by the reviewer using the Review Manager Software
§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Swain 1987	Yes	Yes	No	No	No randomization; not clear if one person's blisters were all treated in the same way

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Low number of events
Inconsistency	0	
Indirectness	-1	Burn blisters instead of friction blisters
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Conclusion	There is limited evidence from 1 experimental study in favour of keeping a blister intact: It was shown in one study that keeping a blister intact resulted in a statistically significant decrease of bacteria/*Staphylococcus aureus* colonisation, compared to aspirating of deroofing a blister (Swain 1987). Evidence is of very low quality and results cannot be considered precise due to limited sample size.
Reference(s)	**Articles** Swain AH, Azadian BS, Wakeley CJ, Shakespeare PG. *Management of blisters in minor burns.* Br Med J (Clin Res Ed). 1987, 295(6591):181

Friction blisters – Compeed (First Aid)

Question (PICO)	In people (P), is using Compeed (I) effective as a first aid intervention for friction blisters (O) compared to not doing this (C)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. compeed:ti,ab,kw OR ((plaster:ti,ab,kw OR plasters:ti,ab,kw OR bandage:ti,ab,kw OR bandages:ti,ab,kw) AND ("second skin":ti,ab,kw)) 2. [mh "blister"] OR blister:ti,ab,kw OR blisters:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for systematic reviews, experimental and observational studies using the following search strategy: 1. compeed[TIAB] OR ((plaster[TIAB] OR plasters[TIAB] OR bandage[TIAB] OR bandages[TIAB]) AND ("second skin"[TIAB])) 2. blister[Mesh] OR blister[TIAB] OR blisters[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) for systematic reviews, experimental and observational studies using the following search strategy: 1. compeed:ab,ti OR ((plaster:ab,ti OR plasters:ab,ti OR bandage:ab,ti OR bandages:ab,ti) AND ("second skin":ab,ti)) 2. blister/exp OR blister:ab,ti OR blisters:ab,ti 3. 1-2 AND
Search date	28 September 2015
In/Exclusion criteria	**Population**: Include: people with blisters or other dermal wounds **Intervention**: Include: Compeed **Comparison:** Include: No compeed or other specific products (creams, spray, plaster) **Outcome**: Include: Direct health-related outcomes relating to blisters/dermal wounds **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomized controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, laboratory studies. **Language:** English. **Publication year:** All years.

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	Not applicable

Friction blisters – Specific socks (Prevention)

Question (PICO)	In people (P), is using specific socks (I) effective to prevent friction blisters (O) compared to usual socks (C)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. sock:ti,ab,kw OR socks:ti,ab,kw 2. [mh "blister"] OR blister:ti,ab,kw OR blisters:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for systematic reviews, experimental and observational studies using the following search strategy: 1. sock[TIAB] OR socks[TIAB] 2. blister[Mesh] OR blister[TIAB] OR blisters[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) for systematic reviews, experimental and observational studies using the following search strategy: 1. sock:ab:ti OR socks:ab:ti 2. blister/exp OR blister:ab,ti OR blisters:ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	08 September 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: wearing specific socks **Comparison:** Include: wearing usual socks **Outcome**: Include: health-related outcomes regarding friction blisters **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies.

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Herring, 1993, USA	Experimental: non-randomized controlled trial	50 runners performing a series of 10 run-trial efforts (between 45-180 minutes) conducted over a 10- to 30-day period	Intervention: acrylic sock (left foot) Control: cotton sock (right foot)	
Knapik, 1996, United Kingdom	Experimental: non-randomized controlled trial	357 male Marine recruits received U.S. Marine recruit training (61 training days over a 12-week period) were divided into 3 groups: wearing standard military boot sock plus a liner sock made of a polyester material (n=106, intervention 1), wearing the polyester liner under a prototype boot sock made of a wool-polyester blend (n=91, intervention 2) or wearing standard military boot socks (n=160, control)	Intervention 1: standard military boot sock plus a liner sock made of a polyester material Intervention 2: polyester liner under a prototype boot sock made of a wool-polyester blend Control: standard military boot socks	Recruit training includes 3 road marches of 5, 8, and 10 miles, 2 endurance courses, the Combat Assault Course and the Combat Conditioning Course, drill periods and numerous unit non-tactical administrative movements.
Van Tiggelen, 2009	Experimental: cluster randomized controlled trial	173 officer cadets of the Belgian Royal Military Academy who wore padded polyester sock (intervention 1, n=53, 15% females), two pairs of socks (intervention 2, n=56, 17% females) or regular army socks (control, n=64, 15% females).	Intervention 1: padded polyester socks (88% polyester, 11% polyamide, 1% elastane) Intervention 2: Two pairs of socks on top of each other comprising a thin inner sock (45% polyester, 45% viscose, 8% polyamide, 2% elastane) Control: regular army socks (70% combing wool and 30% polyamide)	All officer cadets followed the same 6-week basic military training. The number of foot blisters were identified after the end of this training program.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Number of foot blisters	Polyester vs regular army socks	Statistically significant: 15/53 vs 48/64 § RR: 0.38, 95%CI [0.24; 0.59]* (p<0.0001) *in favour of padded polyester socks*	1, 53 vs 64	Van Tiggelen, 2009
	Standard boot sock with liner vs regular army socks	Not statistically significant: 82/106 vs 110/160 § RR: 1.13, 95%CI [0.97; 1.30]* (p=0.11)* ¥	1, 106 vs 160	Knapik, 1996

	Prototype boot sock with liner vs regular army socks	Statistically significant: 36/91 vs 110/160 § RR: 0.58, 95%CI [0.44; 0.76]* (p<0.0001)* *in favour of prototype boot sock with liner*	1, 91 vs 160	
	Two pairs of socks vs regular army socks	Statistically significant: 30/56 vs 48/64 § RR: 0.71, 95%CI [0.54; 0.95]* (p=0.02) *in favour of two pairs of socks*	1, 56 vs 64	Van Tiggelen, 2009
	Acrylic vs cotton socks	Not statistically significant: 34/242 vs 44/242 §, RR: 0.77, 95%CI [0.51;1.16]* (p=0.22) ¥	1, 242 vs 242 (within subjects design)	Herring, 1993

§ Imprecision (low number of events)

* Calculations done by the reviewer(s) using Review Manager software

¥ Imprecision (large variability of results)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Herring, 1993	No randomisation, allocation concealment unclear	No	No	No	
Knapik, 1996	No randomisation, allocation concealment unclear	Unclear	No	No	
Van Tiggelen, 2009	Randomisation, allocation concealment unclear	Unclear	No	No	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Low number of events and large variability of results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is limited evidence in favour of wearing specific socks. It was shown that polyester socks, a prototype boot sock with liner or two pair of socks resulted in a statistically significant decreased risk of foot blisters, compared to wearing regular army socks. (Knapik 1996, Van Tichelen 2009) However, a statistically significant decreased risk of foot blisters, wearing a standard boot sock with liner or acrylic socks compared to regular army socks (Knapik 1996) or cotton socks (Herring 1993), could not be demonstrated. Evidence is of low quality and results cannot be considered precise due the low number of events and/or large variability of results.
Reference(s)	**Articles** Herring KM, Richie DH Jr. *Comparison of cotton and acrylic socks using a generic cushion sole design for runners*. J Am Podiatr Med Assoc. 1993, 83(9):515-522. Knapik JJ, Hamlet MP, Thompson KJ, Jones BH. *Influence of boot-sock systems on frequency and severity of foot blisters.* Mil Med. 1996, 161(10):594-598. Van Tiggelen D, Wickes S, Coorevits P, Dumalin M, Witvrouw E. *Sock systems to prevent foot blisters and the impact on overuse injuries of the knee joint*. Mil Med. 2009, 174(2):183-189.

Friction blisters – Specific products (cream/spray/plaster) (Prevention)

Question (PICO)	In people (P), is using specific creams, sprays or plasters (I) effective to prevent friction blisters (O) compared to not doing this (C)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh emollients] OR [mh ointments] OR [mh antiperspirants] OR [mh skin cream] OR spray:ti,ab,kw OR sprays:ti,ab,kw OR cream:ti,ab,kw OR plaster:ti,ab,kw OR plaster:ti,ab,kw OR emollient*:ti,ab,kw OR ointment*:ti,ab,kw OR antiperspirant*:ti,ab,kw 2. [mh "blister"] OR blister:ti,ab,kw OR blisters:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for systematic reviews, experimental and observational studies using the following search strategy: 1. Emollients[Mesh] OR ointments[Mesh] OR antiperspirants[Mesh] OR "skin cream"[Mesh] OR spray[TIAB] OR sprays[TIAB] OR cream[TIAB] OR plaster[TIAB] OR plaster[TIAB] OR emollient*[TIAB] OR ointment*[TIAB] OR antiperspirant*[TIAB] 2. blister[Mesh] OR blister[TIAB] OR blisters[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) for systematic reviews, experimental and observational studies using the following search strategy: 1. 'emollient agent'/exp OR 'ointment'/exp OR 'antiperspirant agent'/exp OR 'skin cream'/exp OR spray:ab,ti OR sprays:ab,ti OR cream:ab,ti OR plaster:ab,ti OR plaster:ab,ti OR emollient*:ab,ti OR ointment*:ab,ti OR antiperspirant*:ab,ti 2. blister/exp OR blister:ab,ti OR blisters:ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	08 September 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: using specific creams, sprays or plasters. Exclude: using creams/sprays/plasters during extreme sport activities (e.g. ultra-marathons). **Comparison:** Include: no/placebo specific creams, sprays or plasters **Outcome**: Include: number of blisters **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomized controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, laboratory studies.

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Knapik, 1998, USA	Experimental: non-randomized controlled trial	1130 cadets at the US Military Academy. 565 applied an antiperspirant (intervention) and 565 applied a placebo preparation to their feet for 5 consecutive nights. On day 6 a 21-km hike was performed.	Intervention : Antiperspirant (20% aluminium chloride hexahydrate in anhydrous ethyl alcohol) on the entire foot Control: placebo (anhydrous ethyl alcohol) on the entire foot	
Reynolds, 1995, USA	Experimental: randomized controlled trial	23 healthy men (22±2.9 years) walked on a treadmill (5.00 km/h, 1% grade) in a warm environment (28°C, 25% relative humidity). For 4 consecutive days before the walk, the subjects' feet were treated with an antiperspirant (20% aluminium zirconium tetrachlorohydrex glycine concentration plus water) with emollient additives (intervention 1), or nothing (control)	Intervention: antiperspirant (20% aluminium zirconium tetrachlorohydrex glycine concentration plus water) with emollient additives Control: nothing (no treatment)	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Number of foot blisters	Antiperspirant vs placebo	Statistically significant: 105/328 vs 149/339 § RR: 0.73, 95%CI [0.60; 0.89]* (p=0.002) *in favour of antiperspirant*	1, 328 vs 339	Knapik, 1998
	Antiperspirant + emollients vs nothing	Not statistically significant: 9/23 vs 12/23 § RR: 0.75, 95%CI [0.39; 1.43]* ¥ (p=0.38)	1, 23 vs 23	Reynolds, 1995

§ Imprecision (low number of events)

¥ Imprecision (large variability of results)

* Calculations done by the reviewer(s) using Review Manager software

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Knapik 1998	Unclear	No	Yes	No	No randomisation
Reynolds, 1995	Unclear	No	No	No	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Low number of events and large variability in results (Reynolds 1995)
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is limited evidence in favour of using a spray (antiperspirant). In making this evidence conclusion, we place a higher value on the larger study (i.e. more weight, Knapik 1998). It was shown that using an antiperspirant spray resulted in a statistically significant decreased risk of foot blisters, compared to a placebo spray (Knapik 1998). However, in one study, a statistically significant decreased risk of foot blisters, using an antiperspirant spray (+ emollients) compared to no spray, could not be demonstrated (Reynolds 1995). Evidence is of low quality and results cannot be considered precise due to the low number of events and the large variability in results (Reynolds 1995).
Reference(s)	**Articles** Knapik JJ, Reynolds K, Barson J. Influence of an antiperspirant on foot blister incidence during cross-country hiking. J Am Acad Dermatol. 1998, 39(2 Pt 1):202-206. Reynolds K, Darrigrand A, Roberts D, Knapik J, Pollard J, Duplantis K, Jones B. *Effects of an antiperspirant with emollients on foot-sweat accumulation and blister formation while walking in the heat*. J Am Acad Dermatol. 1995, 33(4):626-630.

Friction blisters – Dry socks/shoes (Prevention)

Question (PICO)	In people (P), is wearing dry socks/shoes (I) effective to prevent friction blisters (O) compared to wet socks/shoes (C)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Risk factors"] OR (risk NEXT factor*):ti,ab,kw 2. [mh shoes] OR shoe:ti,ab,kw OR shoes:ti,ab,kw OR sock:ti,ab,kw OR socks:ti,ab,kw 3. wet:ti,ab,kw OR dry:ti,ab,kw OR soaked:ti,ab,kw OR drenched:ti,ab,kw 4. 2 AND 3 5. 1 OR 4 6. [mh "blister"] OR blister:ti,ab,kw OR blisters:ti,ab,kw 7. 5 AND 6 **MEDLINE** (via PubMed interface) for systematic reviews, experimental and observational studies using the following search strategy: 1. "Risk factors"[Mesh] OR risk factor*[TIAB] 2. shoes[Mesh] OR shoe[TIAB] OR shoes[TIAB] OR sock[TIAB] OR socks[TIAB] 3. wet[TIAB] OR dry[TIAB] OR soaked[TIAB] OR drenched[TIAB] 4. 2 AND 3 5. 1 OR 4 6. blister[Mesh] OR blister[TIAB] OR blisters[TIAB] 7. 5 AND 6 **Embase** (via Embase.com interface) for systematic reviews, experimental and observational studies using the following search strategy:

	1. 'risk factor'/exp OR (risk NEXT/1 factor*):ab,ti 2. shoes/exp OR shoe:ab,ti OR shoes:ab,ti OR sock:ab,ti OR socks:ab,ti 3. wet:ab,ti OR dry:ab,ti OR soaked:ab,ti OR drenched:ab,ti 4. 2 AND 3 5. 1 OR 4 6. blister/exp OR blister:ab,ti OR blisters:ab,ti 7. 5 AND 6 Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	08 September 2015
In/Exclusion criteria	**Population**: Include: people with friction blisters or healthy volunteers of all ages. **Intervention**: Include: wearing dry socks/shoes **Comparison:** Include: wearing wet socks/shoes **Outcome**: Include: number of blisters, rate of foot temperature change (indirect outcome) **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies.

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Kirkham, 2014, United Kingdom	Experimental: randomized controlled trial (within-subjects design)	20 healthy individuals (10 male, 10 female) aged 18 years and over (median age: 23.5 years) were recruited from staff and students at the University of Salford, UK. The skin on one foot was unhydrated (intervention) whereas the other foot was hydrated by soaking the foot in water (control)	Intervention: foot remained exposed to the environment (unhydrated) Control: foot hydration in water at a room temperature for 5 minutes	Intermittent loading was carried out until an observable change of 3°C was evident using infrared thermography

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Rate of temperature change (°C/min)	Unhydrated versus hydrated foot	Statistically significant: 0.57 (5.64) vs 1.175 (5.23) (median and interquartile range) Median difference: -0.605 £ (p=0.001) *In favour of unhydrated foot*	1, 20 vs 20 § (within-subjects design)	Kirkham, 2014

£ No CI available

§ Imprecision (limited sample size)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Kirkham, 2014	Randomisation, allocation concealment unclear	Unclear	No	No	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Limited sample size
Inconsistency	0	
Indirectness	-1	Rate of temperature change as an indirect outcome for blister creation
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is limited evidence in favour of dry feet. It was shown that unhydrated feet resulted in a statistically significant decreased rate of temperature change of the skin in response to load application, compared to hydrated feet (Kirkham 2014). Evidence is of low quality and results cannot be considered precise due to the limited sample size.
Reference(s)	**Articles** Kirkham S, Lam S, Nester C, Hashmi F. *The effect of hydration on the risk of friction blister formation on the heel of the foot*. Skin Res Technol. 2014, 20(2):246-253.

Strains and sprains – Ice (First Aid)

Question (PICO)	In humans with strains or sprains (P), is ice (I) compared to no ice (C) effective to improve health outcomes (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Sprains and strains"] OR [mh "Soft Tissue Injuries"] OR "muscle strain":ti,ab,kw OR "ligament sprain*":ti,ab,kw 2. [mh Ice] OR [mh cryotherapy] OR Ice:ti,ab,kw OR cryotherapy:ti,ab,kw OR "cold therapy":ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Sprains and strains"[Mesh] OR "Soft Tissue Injuries"[Mesh] OR muscle strain*[TIAB] OR ligament sprain*[TIAB] 2. Ice[Mesh] OR cryotherapy[Mesh:NoExp] OR Ice[TIAB] OR cryotherapy[TIAB] OR cold therapy[TIAB] 3. 1-2 AND 4. ((((("ice"[MeSH Terms] OR ice[Text Word]) OR ("cold therapy"[Text Word]) OR ("Cryotherapy"[Mesh:noexp])) AND ((((("ankle injuries"[TIAB] NOT Medline[SB]) OR "ankle injuries"[MeSH Terms] OR ankle injury[Text Word] OR ankle injuries[tw]) OR ("ankle joint"[MeSH Terms] OR ankle joint[Text Word] OR ankle joints[tw]) OR ("lateral ligament, ankle"[MeSH Terms] OR ankle lateral ligament[Text Word] OR ankle lateral ligaments[tw])) OR ((((("sprains and strains"[TIAB] NOT Medline[SB]) OR "sprains and strains"[MeSH Terms] OR sprain[Text Word] OR sprains[tw]) OR (distortion[tw] OR distortions[tw]) OR ("Rupture"[Mesh:noexp] OR rupture[tw] OR ruptures[tw])) AND

	("ankle"[MeSH Terms] OR ankle[Text Word] OR ankles[tw])) AND ((Humans[Mesh]) AND (adult[MeSH]))) AND ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading]) AND ((Humans[Mesh]) AND (adult[MeSH])) 5. 3-4 NOT **Embase** (via Embase.com interface) using the following search strategy: 1. 'sprain'/exp OR 'ligament injury'/exp OR 'soft tissue injury'/exp OR 'muscle strain':ab,ti OR 'ligament sprain':ab,ti 2. 'ice'/exp OR 'cryotherapy'/exp OR ice:ab,ti OR cryotherapy:ab,ti OR 'cold therapy':ab,ti 3. 1-2 AND **Cinahl** using the following search strategy: 1. (MH "Sprains and Strains+") OR (MH "Soft Tissue Injuries+") OR TI "muscle strain*" OR AB "muscle strain*" OR TI ligament sprain* OR AB ligament sprain* 2. (MH Ice) OR (MH cryotherapy) OR TI Ice OR AB Ice OR TI cryotherapy OR AB cryotherapy OR TI cold therapy OR AB cold therapy 3. 1-2 AND Guidelines, systematic reviews, retrieved with the above searches, and used as source for individual studies: van den Bekerom, 2012 IFAG, 2014 Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	5 November 2014
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). We included studies that used ice or a combination of ice with rest, compression and/or elevation as an intervention. Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Comparison**: Include: no ice, with or without rest, compression and/or elevation. **Outcome**: Include: functional recovery, pain, swelling, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values.

	Language: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Basur, 1976, UK	Experimental: Randomized controlled trial	60 patients (10-30 years old) with an ankle injury. 30 patients were assigned to the intervention and 30 to the control group	1. Intervention: cooling ("ice") for first 48 hrs followed by crêpe bandaging 2. Control: only crêpe bandaging	
Laba, 1989	Experimental: Quasi-randomized controlled trial	30 patients, 13-56 years old with acute ankle sprain 14 patients received the intervention, 16 patients were assigned to the control group.	1. Intervention: ice 2. Control: no ice	
Prins, 2011, The Netherlands	Experimental: Randomized controlled trial	19 participants (6 males, 13 females) recruited within 6 hours after onset of calf muscle rupture 10 people (mean age 39.9±7.0) received the intervention, 9 patients (mean age 43.4±6.7) were assigned to the control group.	1. Intervention: plastic bag with crushed ice fixed with compression bandage applied for minimum 20 min and max 30 min 2. Control group: no ice and no compression bandage	
Sloan, 1989, UK	Experimental: Randomized controlled trial	143 patients (79% male), 16-50 years, with acute ankle sprain	1. Intervention: cold therapy ("ice"): application of cooling anklet inflated to 30 mmHg for 30 min + elevation of ankle 2. Control: dummy therapy: application of non-inflated anklet without elevation	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Recovery	1. Cooling and crêpe bandaging 2. Only crêpe bandaging	Not statistically significant: After 2 days: 42.1% vs 29.1% Difference: 13.0% (p>0.05) †£ <u>Statistically significant:</u> After 7 days: 84.2% vs 60.6% Difference: 23.6% (p<0.05) £ *In favour of cooling* Not statistically significant: After 14 days: 96.2% vs 88.2% Difference: 8.0% (p>0.05) £	1, 30 vs 30 §	Basur, 1976

Pain after treatment, measured on day of discharge (yes/no)	Ice vs no ice	<u>Statistically significant:</u> Mild pain: 3/14 vs 11/16 RR: 0.31, 95%CI [0.11; 0.90] (p=0.03)* *In favour of ice* No pain: 4/14 vs 12/16 RR: 0.38, 95%CI [0.16; 0.91] (p=0.03)* *In favour of ice*	1, 14 vs 16 §	Laba, 1989
Pain in rest (change 0-6 days) (VAS)	1. Intervention: ice and compression 2. Control: no ice and no compression	Not statistically significant: -1.6±1.4 vs -3.2±2.1 (p=0.34)	1, 10 vs 9 §	Prins, 2011
Pain while walking (change 0-6 days) (VAS)		Not statistically significant: -4.2±3.1 vs -4.0±2.7 (p=0.96) †£		
Pain while running (change 0-6 days) (VAS)		Not statistically significant: -2.1±2.5 vs -2.1±3.8 (p=0.25) †£		
Functional capacity (DVL-LEFS score)		Not statistically significant: 28.8±8.7 vs 23.9±17.7 MD: 4.90, 95%CI[-7.86; 17.66]* (p=0.86) ¥		
Length of functional reconvalescence period		Not statistically significant: 34.6±16.2 vs 43.8±40.5 MD: -9.20, 95%CI[-37.50; 19.10]* (p=1.00) ¥		
Length of work absenteeism period (days)		Not statistically significant: 3.0±4.9 vs 2.6±5.1 MD: 0.4, 95%CI[-4.11; 4.91]* (p=1.00) ¥		
Soft tissue swelling	Cold therapy vs dummy therapy	Not statistically significant: 46% vs 40% (p=0.07) †£	1, 143 (not mentioned how many in each group) §	Sloan, 1989
Ability to bear weight		Not statistically significant: 36% vs 29% (p=0.64) †£		

Mean±SD (unless stated otherwise)
* Calculations done by the reviewer(s) using Review Manager software
£ No raw data/SD's available, effect size and/or CI cannot be calculated
¥ Imprecision (large variability of results)
† Imprecision (lack of data)
§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Basur, 1976	Unclear, not mentioned	Unclear, not mentioned	Yes, only recovery period, nothing on pain or swelling	No	
Laba, 1989	No, allocation by coin toss	Yes, it was known to the investigators to which group a patient was assigned	No	No	

Prins, 2011	No, allocation based on computerized random number generator	No, participants were not blinded, but outcome assessors were blinded	No	No	
Sloan, 1989	No, allocated based on predetermined sequence	No, double blind study	No	No	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/lack of data/large variability of the results
Inconsistency	0	
Indirectness	-1	Hospital setting for most studies
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [D]**	

Conclusion	There is limited evidence in favour of ice/cooling. [In making this evidence conclusion, we place a higher value on the significant outcomes of recovery and pain on discharge over the outcomes of swelling and ability to bear weight for which an effect could not be shown.] It was shown that ice/cooling resulted in a statistically significant decrease in recovery after 7 days and pain after treatment, compared to no ice/cooling (Basur 1976, Laba 1989). However, a statistically significant increase of soft tissue swelling and ability to bear weight, using cold therapy compared to dummy therapy, could not be demonstrated (Sloan 1989). In case of using a combination of ice and compression, a statistically significant decrease of pain in rest, while walking and while running, functional capacity and length of functional reconvalescence period, compared to no treatment, could not be demonstrated (Prins 2011). Evidence is of low quality and results of these studies are imprecise due to limited sample size or low number of events, lack of data and large variability of results.
Reference(s)	**Articles** Basur RL, ShephardE, Mouzas GL. *A cooling method in the treatment of ankle sprains*. Practioner 1976; 216(1296):708-11 Laba E, Roestenburg M. *Clinical evaluation of ice therapy for acute ankle sprain injuries*. New Zealand Journal of Physiotherapy 1989; 17(2):7-9 Prins JC, Stubbe JH, van Meeteren NL, Scheffers FA, van Dongen MC. *Feasibility and preliminary effectiveness of ice therapy in patients with an acute tear in the gastrocnemius muscle: a pilot randomized controlled trial*. Clin Rehabil 2011; 25(5):433-41 Sloan JP, Hain R, Pownall R. *Clinical benefits of early cold therapy in accident and emergency following ankle sprain*. Arch Emerg Med 1989; 6(1):1-6 **Systematic reviews** van den Bekerom MP, Struijs PA, Blankevoort L, Welling L, van Dijk CN, Kerkhoffs GM. *What is the evidence for rest, ice, compression, and elevation in the treatment of ankle sprains in adults?* J Athl Train 2012; 47(4):435-43

Sprains and strains – Rest (First Aid)

Question (PICO)	In humans with strains and sprains (P), is rest (I) compared to no rest (C) effective to improve health outcomes (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Sprains and strains"] OR [mh "Soft Tissue Injuries"] OR "muscle strain":ti,ab,kw OR "ligament sprain*":ti,ab,kw 2. [mh "Restraint, Physical"] OR [mh "Restraint, Physical"] OR [mh immobilization] OR [mh Rest] OR physical restraint:ti,ab,kw OR immobilization:ti,ab,kw OR immobilization:ti,ab,kw OR rest:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Sprains and strains"[Mesh] OR "Soft Tissue Injuries"[Mesh] OR muscle strain*[TIAB] OR ligament sprain*[TIAB] 2. "Restraint, Physical"[Mesh] OR immobilization[Mesh:NoExp] OR Rest[Mesh] OR physical restraint[TIAB] OR immobilization[TIAB] OR immobilization [TIAB] OR rest[TIAB] 3. 1-2 AND 4. ((((((“ankle injuries”[TIAB] NOT Medline[SB]) OR “ankle injuries”[MeSH Terms] OR ankle injury[Text Word] OR ankle injuries[tw]) OR (“ankle joint”[MeSH Terms] OR ankle joint[Text Word] OR ankle joints[tw]) OR (“lateral ligament, ankle”[MeSH Terms] OR ankle lateral ligament[Text Word] OR ankle lateral ligaments[tw])) OR (((((“sprains and strains”[TIAB] NOT Medline[SB]) OR “sprains and strains”[MeSH Terms] OR sprain[Text Word] OR sprains[tw]) OR (distortion[tw] OR distortions[tw]) OR (“Rupture”[Mesh:noexp] OR rupture[tw] OR ruptures[tw])) AND (“ankle”[MeSH Terms] OR ankle[Text Word] OR ankles[tw]))) AND ((“Restraint, Physical”[Mesh:noexp] OR “physical restraint”[tw]) OR (“Immobilization”[Mesh:noexp] OR immobilizat*[tw]) OR (mobilizat*[tw])) AND ((adult[MeSH])))) AND ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading]) AND ((adult[MeSH])) 5. 3-4 NOT **Embase** (via Embase.com interface) using the following search strategy: 1. ‘sprain’/exp OR 'ligament injury'/exp OR 'soft tissue injury'/exp OR 'muscle strain':ab,ti OR ‘ligament sprain’:ab,ti 2. 'rest'/exp OR 'physical restraint':ab,ti OR immobilization:ab,ti OR immobilisation:ab,ti OR rest:ab,ti 3. 1-2 AND **Cinhal**: 1. (MH "Sprains and Strains+") OR (MH "Soft Tissue Injuries+") OR TI “muscle strain*” OR AB “muscle strain*” OR TI ligament sprain* OR AB ligament sprain* 2. (MH "Restraint, Physical") OR (MH Immobilization) OR TI “physical restraint” OR AB “physical restraint” OR TI immobilization OR AB immobilization OR TI immobilisation OR AB immobilisation OR TI rest OR AB rest 3. 1-2 AND Guidelines, systematic reviews, retrieved with the above searches, and used as source for individual studies: Jones, 2007 Kerkhoffs, 2002

	Kerkhoffs, 2012 van den Bekerom, 2012
Search date	5 November 2014
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Immobilization by plaster cast was included as an intervention for "rest", but considered as indirect evidence. Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: functional recovery, pain, swelling, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Bleakley, 2010, UK	Experimental: Randomized controlled trial	101 patients (69 men, 32 women) aged 16-65 years with an acute (<7days) grade 1 or 2 ankle sprain. 51 patients received standard treatment, 50 patients received exercise treatment. Analysis based on intention to treat.	1) Standard treatment ("rest"): protection, rest, ice, compression and elevation 2) Exercise treatment: ice and compression + therapeutic exercises Duration of treatment: 4 weeks	Sample size was calculated (60 participants in each group to obtain 80% power with α=0.05)
Caro, 1964, UK	Experimental: Randomized controlled trial	132 patients (all ages) with inversion injury of the ankle. 42 patients received strapping by elastic bandage, 37 patients received a Plaster-of-Paris	1) Plaster-of-Paris ("rest"): standard technique using a back slab and incorporating a rocker. Patients were allowed to bear weight fully 48 hours	

			after application. The plaster was left on for two weeks. 2) Strapping: Elastic adhesive bandage, patients were encouraged to bear weight, but advised to keep foot raised when not walking and to do gentle exercises.	
Eiff, 1994, USA	Experimental: Randomized controlled trial	Patients aged 16-50 years with lateral ankle sprains. 40 patients were assigned to the early mobilization group, 37 patients were assigned to the immobilization group	1) Immobilization group ("rest"): Plaster splint + avoid any weight bearing for 10 days. 2) Early mobilization group: ankle was wrapped with elastic bandage for 48h. On day 3, a pneumatic compression brace was fitted (until day 10) and patients were advised to resume usual activities as tolerated. Patients were instructed to follow standard rehabilitation exercises. Both groups: ice and elevation as much as possible for first 48 hours.	
Hedges, 1980, USA	Experimental: Quasi-randomized controlled trial	157 patients (68 male, 89 female) aged 15-65 years with ankle injury. 44 patients were assigned to the early mobilization group, 49 received a splint	1) Splint group ("rest"): plaster posterior splint applied. Patients were instructed not to attempt to bear weight. 2) Early mobilization group: elastic bandage applied to ankle, fitted with pair of crutches. Ice pack to injured area for next 24-48hrs. Elevation was encouraged, as was early mobilization using crutches.	
Roycroft, 1983, Ireland	Experimental: randomized controlled trial	98 patients with inversion injuries of the ankle. 37 patients received conservative treatment, 43 received immediate active treatment.	1) Conservative treatment ("rest"): wool and Elastoplast bandage or plaster of Paris backslab. Advised to use crutches to be non-weight-bearing.	

			2) Active treatment: Cold packs + elevation + crepe bandage to aid compression. Patients were encouraged to bear weight fully. This treatment was repeated after 24 hours	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Ankle function (score 0-80 ± SD)	Exercise vs standard treatment ("rest")	Week 1: Statistically significant: 57.9±14.4 vs 52.1±14.7 Baseline adjusted MD: 5.28, 95%CI [0.31;10.26] (p=0.008) *In favour of exercise* Week 2: Statistically significant: 68.6±8.8 vs 61.8±13.3 Baseline adjusted MD: 4.92, 95%CI [0.27; 9.57] (p=0.0083) *In favour of exercise* Week 3: Not statistically significant: 71.5±8.6 vs ± 69.1±10.4 MD: 2.4, 95%CI [-1.32; 6.12] (p=0.21)* Week 4: Statistically significant: 74.9±7.0 vs ± 71.9±8.0 MD: 3.0, 95%CI [-0.07; 5.93] (p=0.04)* *In favour of exercise*	1, 50 vs 51 §	Bleakley, 2010
Pain at rest (10cm VAS)		Week 1: Not Statistically significant: 6.2±7.85 vs 10.3±13.0 MD: -4.10, 95%CI [-8.28; 0.08] (p=0.05)* ¥ Week 2: Not Statistically significant: 3.6±5.8 vs 5.9±11.0 MD: -2.30, 95%CI [-5.72; 1.12] (p=0.19)* ¥ Week 3: Not statistically significant: 2±4.1 vs ± 3.1±5.8 MD: -1.10, 95%CI [-3.06; 0.86] (p=0.27)* ¥		

		Week 4: Not Statistically significant: 1.9±6.44 vs ± 1.7±3.2 MD: 0.20, 95%CI [-1.79; 2.19] (p=0.84)* ¥		
Pain on activity (10 cm VAS)		Week 1: Not Statistically significant: 28.9±21.8 vs 33.5±19.9 MD: -4.60, 95%CI [-13.10; 3.90] (p=0.29)* Week 2: Not Statistically significant: 20.1±20.1 vs 18.7±14.4 MD: 1.40, 95%CI [-5.43; 8.23] (p=0.69)* Week 3: Not statistically significant: 12.3±15.4 vs 11.9±11.2 MD: 0.40, 95%CI [-4.86; 5.66] (p=0.88)* Week 4: Not Statistically significant: 9.5±15.4 vs 8.9±12.8 MD: 0.60, 95%CI [-4.93; 6.13] (p=0.83)* ¥		
Swelling (cm)		Week 1: Not Statistically significant: 1.0±1.3 vs 1.0±1.5 MD: 0.00, 95%CI [-0.55; 0.55] (p=1.00)* ¥ Week 2: Not Statistically significant: 0.7±1.0 vs 0.6±0.8 MD: 0.10, 95%CI [-0.25; 0.45] (p=0.58)* ¥ Week 3: Not statistically significant: 0.8±0.7 vs 1.0±0.9 MD: -0.20, 95%CI [-0.51; 0.11] (p=0.21)* ¥ Week 4: Not Statistically significant: 0.4±1.0 vs 0.7±1.3 MD: -0.30, 95%CI [-0.75; 0.15] (p=0.19)* ¥		
Number of participants returning to work	Immobilization (“rest”) vs mobilization	Statistically significant: 10 days follow-up: 4.81/37 (13%) vs 21.6/40 (54%) OR: 0.24, 95%CI [0.14; 0.41] (p<0.00001)*	1, 37 vs 40 §	Eiff, 1994

		In favour of mobilization Not statistically significant: <u>3 weeks follow-up:</u> 29.23/37 (79%) vs 30/40 (75%) OR: 1.05, 95%CI [0.91; 1.23] (p=0.50)* Not statistically significant: <u>6 weeks follow-up:</u> 35.52/37 (96%) vs 38.8/40 (97%) OR: 0.99, 95%CI [0.94; 1.04] (p=0.70)*		
Time to recovery (days)	Plaster-of-Paris ("rest") vs strapping	<u>Statistically significant:</u> 25.3±8.27 vs 20.0±11.01 MD: 5.30, 95%CI [1.04, 9.56] (p=0.01)* *In favour of strapping*	1, 37 vs 42 §	Caro, 1964
	Conservative treatment ("rest") vs active treatment	<u>Statistically significant:</u> 18.6 vs 11.9 (p<0.005) †£ *In favour of active treatment*	1, 37 vs 43 §	Roycroft, 1983
Pain	Immobilization vs mobilization	<u>10 days follow-up:</u> Not statistically significant: 28.86/37 (78%) vs 32.4/40 (81%) OR: 0.96, 95%C I[0.84; 1.11] (p=0.60)* <u>3 weeks follow-up:</u> <u>Statistically significant:</u> 32.19/37 (87%) vs 22.8/40 (57%) OR: 1.53, 95%CI [1.27; 1.84] (p<0.00001)* *In favour of mobilization* <u>6 weeks follow-up:</u> Not statistically significant: 22.94/37 (62%) vs 19.2/40 (48%) OR: 1.29, 95%CI [1.00; 1.67] (p=0.05)*¥ <u>3 months follow-up:</u> Not statistically significant: 8.88/37 (24%) vs 10.4/40 (26%) OR: 1.08, 95%CI[0.92; 1.49] (p=0.74)*¥ <u>6 month follow-up:</u> Not statistically significant: 4.44/37 (12%) vs 4/40 (10%) OR: 1.20, 95%CI [0.54; 2.65] (p=0.65)*¥	1, 37 vs 40 §	Eiff, 1994

Swelling		Not statistically significant: <u>10 days follow-up:</u> 31.08/37 (84%) vs 33.6/40 (85%) OR: 0.99, 95%CI [0.88; 1.11] (p=0.85)* <u>3 weeks follow-up:</u> 25.16/37 (68%) vs 22/40 (55%) OR: 1.24, 95%CI [0.99; 1.54] (p=0.06)*¥ <u>6 weeks follow-up:</u> 16.28/37 (44%) vs 12.8/40 (32%) OR: 1.38, 95%CI [0.96; 1.97] (p=0.08)*¥ <u>3 months follow-up:</u> 5.55/37 (15%) vs 4.4/40 (11%) OR: 1.36, 95%CI [0.66; 2.82] (p=0.40)*¥ <u>6 month follow-up:</u> 1.11/37 (3%) vs 1.2/40 (3%) OR: 1.00, 95%CI [0.21; 4.84] (p=1.00)*¥		
Weight bearing (0-4)	Immobilization by splint ("rest") vs early mobilization	Not statistically significant: <u>After 1 week:</u> 2.04±1.54 vs 2.20±1.39 MD: -0.16, 95%CI [-0.76; 0.44] (p=0.60)*	1, 49 vs 44 §	Hedges, 1980
Pain (0-4)		Not statistically significant: <u>After 1 week:</u> -2.08±1.26 vs -1.84±1.22 MD: -0.24, 95%CI [-0.74; 0.26] (p=0.35)*		
Swelling (cm)		Not statistically significant: <u>After 1 week:</u> -0.51±0.58 vs -0.34±0.64 MD: -0.17, 95%CI [-0.42; 0.08] (p=0.18)*¥		

mean±SD (unless stated otherwise)
*Calculations done by the reviewer(s) using Review Manager software
¥ Imprecision (large variability of results)
† Imprecision (lack of data)
§ Imprecision (limited sample size or low number of events)
£ No raw data available, effect size and CI cannot be calculated.

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Bleakley, 2010	No, opaque sealed envelope	No, outcome assessor was blinded	No	No	Imprecision (limited sample size (smaller than calculated sample size))
Caro, 1964	Unclear, "random assignment", but not specified how	Yes, but not relevant	Yes (nothing on pain or swelling)	No	Imprecision (limited sample size)

Eiff, 1994	unclear, not specified in the article	Unclear, not specified in the article	no	no	Imprecision (limited sample size)
Hedges, 1980	No, patients were allocated to a treatment group based on file number (even/uneven)	Yes, patients were grouped based on file number (even/uneven)	no	no	Imprecision (limited sample size)
Roycroft, 1983,	Unclear, not specified	Unclear, not specified	Yes, only recovery period mentioned	No	Imprecision (lack of data, limited sample size)

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/lack of data/large variability of the results
Inconsistency	0	
Indirectness	-1	Immobilization by plaster cast
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Conclusion	There is limited evidence in favour of mobilization. [In making this evidence conclusion, we place a higher value on the significant outcomes of ankle function, number of participants returning to work and time to recovery over the outcomes of pain, swelling and weight bearing for which an effect could not be shown.] It was shown that exercise treatment resulted in a statistically significant increase in ankle function, compared to standard treatment (Bleakley 2010). It was shown that mobilization resulted in a statistically significant increase in participants returning to work after 10 days, and a statistically significant decrease in pain, compared to immobilization (Eiff 1994). It was shown that strapping with weight bearing and exercises or active treatment resulted in a statistically significant decrease in time to recovery, compared to plaster-of-Paris or conservative treatment (Caro 1964, Roycroft 1983). However, a statistically significant change in pain at rest or on activity, using exercise treatment compared to standard treatment, could not be demonstrated (Bleakley 2010). Also, a statistically significant change in swelling and weight bearing, using immobilization compared to mobilization, could not be demonstrated (Bleakley 2010, Eiff 1994, Hedges 1980). Evidence is of very low quality and results of these studies are imprecise due to limited sample size, lack of data and/or large variability of results.
Reference(s)	**Articles** Bleakley CM, O'Connor SR, Tully MA, Rocke LG, MacAuley DC, Bradbury I, Keegan S, McDonough SM. *Effect of accelerated rehabilitation on function after ankle sprain: randomised controlled trial*. BMJ 2010; 340:c1964 Caro D, Craft IL, Howells JB, Shaw PC. *Diagnosis and treatment of injury of lateral ligament of the ankle joint.* Lancet 1964; 2(7362):720-3 Eiff MP, Smith AT, Smith GE. *Early Mobilization Versus Immobilization in the Treatment of Lateral Ankle Sprains*. Am J Sports Med 1994; 22(1):83-88 Hedges JR, Anwar RA. *Management of ankle sprains*. Ann Emerg Med 1980; 9(6):298-302 Roycroft S, Mantgani AB. *Treatment of inversion injuries of the ankle by early active management*. Physiotherapy 1983; 69(10):355-6 **Systematic reviews**

	Jones MH, Amendola AS. *Acute treatment of inversion ankle sprains: immobilization versus functional treatment.* Clin Orthop Relat Res 2007; 455:169-72 Kerkhoffs GM, Rowe BH, Assendelft WJ, Kelly K, Struijs PA, van Dijk CN. *Immobilisation and functional treatment for acute lateral ankle ligament injuries in adults.* Cochrane Database Syst Rev 2002; (3):CD00762 van den Bekerom MPJ, Struijs PAA, Blankevoort L, Welling L, van Dijk CN, Kerkhoffs GMMJ. *What is the Evidence for Rest, Ice, Compression, and Elevation Therapy in the Treatment of Ankle Sprains in Adults?* J Athl Train 2012; 47(4):435-443

Strains and sprains – Compression (First Aid)

Question (PICO)	In humans with strains or sprains (P), is compression (I) compared to no compression (C) effective to improve health outcome measures?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Sprains and strains"] OR [mh "Soft Tissue Injuries"] OR "muscle strain":ti,ab,kw OR "ligament sprain*":ti,ab,kw 2. [mh "Compression Bandages"] OR compress*:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Sprains and strains"[Mesh] OR "Soft Tissue Injuries"[Mesh] OR muscle strain*[TIAB] OR ligament sprain*[TIAB] 2. "Compression Bandages"[Mesh] OR ((compression [TIAB] OR elastic[TIAB]) AND bandage*[TIAB]) 3. 1-2 AND 4. (((compress*) AND ((((“ankle injuries”[TIAB] NOT Medline[SB]) OR “ankle injuries”[MeSH Terms] OR ankle injury[Text Word] OR ankle injuries[tw]) OR (“ankle joint”[MeSH Terms] OR ankle joint[Text Word] OR ankle joints[tw]) OR (“lateral ligament, ankle”[MeSH Terms] OR ankle lateral ligament[Text Word] OR ankle lateral ligaments[tw])) OR ((((“sprains and strains”[TIAB] NOT Medline[SB]) OR “sprains and strains”[MeSH Terms] OR sprain[Text Word] OR sprains[tw]) OR (distortion[tw] OR distortions[tw]) OR (“Rupture”[Mesh:noexp] OR rupture[tw] OR ruptures[tw])) AND (“ankle”[MeSH Terms] OR ankle[Text Word] OR ankles[tw]))) AND ((Humans[Mesh]) AND (adult[MeSH])))) AND ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading]) AND ((Humans[Mesh]) AND (adult[MeSH])) 5. 3-4 NOT **Embase** (via Embase.com interface) using the following search strategy: 1. ‘sprain’/exp OR 'ligament injury'/exp OR 'soft tissue injury'/exp OR 'muscle strain':ab,ti OR ‘ligament sprain’:ab,ti 2. 'compression bandage'/exp OR ((compression:ab,ti OR elastic:ab,ti) AND bandage:ab,ti) 3. 1-2 AND **Cinahl** using the following search strategy: 1. (MH "Sprains and Strains+") OR (MH "Soft Tissue Injuries+") OR TI “muscle strain*” OR AB “muscle strain*” OR TI ligament sprain* OR AB ligament sprain* 2. (MH "Elastic Bandages") OR TI compress* OR AB compress* 3. 1-2 AND

	Guidelines, systematic reviews, retrieved with the above searches, and used as source for individual studies: van den Bekerom, 2012 IFAG, 2014 Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	5 November 2014
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: functional recovery, pain, swelling, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
O'Connor, 2011, Ireland	Experimental: randomized controlled trial	60 patients with acute ankle injury 20 patients were treated with tubigrip bandage (mean age 30.3 years, 66% male), 20 patients with elastoplasts bandage (mean age 31.8 years, 70% male), and 20patients received no support (mean age 26.4 years, 56% male). Intention to treat analysis	1. Tubigrip bandage ("compression") 2. Elastoplast bandage ("compression") 3. No support	A sample size of 16 in each treatment group had an estimated power of 80% to detect a mean difference of 15 Karlsson scores on average

Rucinski, 1991, USA	Experimental: randomized controlled trial	30 individuals (26 men and 4 women, age 18-28 years) with sprained ankles. 10 patients received an elastic wrap, 10 received intermittent compression and 10 were treated with elevation only.	1. Elastic wrap ("compression"): ace wrap was applied, foot elevated 45° for 30 minutes 2. Intermittent compression ("compression device"): a nylon, single cell, lower leg pneumatic appliance applied to injured ankle, foot elevated 45° for 30 minutes 3. Control: only elevation: foot elevated 45° for 30 minutes	
Thorsson, 1997, Sweden	Experimental: non-randomized controlled trial	40 subjects, aged 17-49 years (mean age 28.6) with acute ankle injury 19 subjects received compression treatment, 21 subjects received no treatment.	1. "Compression": immediate treatment with compression bandage 2. Control: no immediate treatment	
Watts, 2001, UK	Experimental: randomized controlled trial	485 patients with grade I or II lateral ankle sprain. 200 were treated with double Tubigrip, 200 received no double Tubigrip.	1. Double Tubigrip ("compression") 2. No double Tubigrip Analgesia and rehabilitation advice were standardised between the two groups by means of an advice sheet which described exercises and advised simple analgesia if necessary	study was set up to detect a 10% difference in outcome between the two treatment groups

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Return to work (days)	1. Tubigrip 2. Elastoplast 3. No compression (no support)	Not statistically significant: 1 vs 3: 5.2±4.9 vs 5.8±4.7 MD: -0.60, 95%CI [-3.83, 2.63] (p=0.72)* ¥ 2 vs 3: 3.7±3.5 vs 5.8±4.7 MD: -2.10, 95%CI [-4.97, 0.77] (p=0.15)* ¥	1, 18 vs 20 vs 16	O'Connor, 2011
	1. Compression (double Tubigrip) 2. No compression (no double Tubigrip)	Not statistically significant: 3.37±2.33 vs 3.21±2.02 MD: 0.16, 95%CI [-0.70, 1.02] (p=0.94)	1, 102 vs 92 §	Watts, 2001
Pain improvement (VAS score)	1. Tubigrip 2. Elastoplast 3. No support	Not statistically significant: 1 vs 3: 2.9±2.5 vs 3.1±1.9 MD: -0.20, 95%CI [-1.68, 1.28] (p=0.79)* ¥	1, 18 vs 20 vs 16	O'Connor, 2011

		2 vs 3: 3.2±2.0 vs 3.1±1.9 MD: 0.10, 95%CI [-1.25, 1.45] (p=0.88)*		
Pain (awake at night) (yes/no)	1. Compression (double Tubigrip) 2. No compression (no double Tubigrip)	Not statistically significant: 54/102 vs 44/92 RR: 1.11, 95%CI [0.84, 1.47] (p=0.48)* ¥	1, 102 vs 92	Watts, 2001
Pain (need for painkillers) (yes/no)		<u>Statistically significant:</u> 81/102 vs 50/92 RR: 1.46, 95%CI [1.18, 1.81] (p=0.0004)* *In favour of no compression*		
Ankle joint function (Karlsson score)	1. Tubigrip 2. Elastoplast 3. No support	Not statistically significant: At 10 days: 1 vs 3: 44.9±20.6 vs 47.8±23.0 MD: -2.90, 95%CI [-17.65, 11.85] (p=0.70)* 2 vs 3: 49.4±17.8 vs 47.8±23.0 MD: 1.60, 95%CI [-12.11, 15.31] (p=0.82)* At 30 days: 1 vs 3: 52.9±17.2 vs 56.3±18.3 MD: -3.40, 95%CI [-15.38, 8.58] (p=0.58)* 2 vs 3: 58.5±16.0 vs 56.3±18.3 MD: 2.20, 95%CI [-9.42, 13.82] (p=0.71)*	1, 18 vs 20 vs 16	O'Connor, 2011
Edema: Ankle volume change (mL)	1. Elastic wrap 2. Intermittent compression device 3. Control (no compression)	<u>Statistically significant:</u> 1 vs 3: 7.4±5.9 vs -14.9±13.7 MD: 22.30, 95%CI [13.13, 31.47] (p<0.00001)* *In favour of no compression* 2 vs 3: 3.7±14.6 vs -14.9±13.7 MD: 18.60, 95%CI [6.19, 31.01] (p=0.003)* *In favour of no compression*	1, 30 (10 in each group) §	Rucinski, 1991
Recovery time (days)	1. Compression 2. Control (no compression)	Not statistically significant: 20.0±14 vs 25±26 MD: -5.00, 95%CI [-17.78, 7.78] (p=0.44)*	1, 19 vs 21 §	Thorsson, 1997

Mean±SD (unless stated otherwise)

*Calculations done by the reviewer(s) using Review Manager software

¥ Imprecision (large variability of results)

§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
O'Connor, 2011	No, randomization by computer generated randomization sequence	No, patients were not blinded to treatment, but outcome was blinded (patients were asked to remove their support before review)	No	No	No imprecision (sample size was calculated)
Rucinski, 1991	Unclear, not specified	Unclear, not mentioned	Yes, nothing on pain or recovery period	No	Imprecision due to sample size
Thorsson, 1997	Yes, not randomized	Yes, not blinded	Yes, nothing on swelling and pain	No	Imprecision (limited sample size)
Watts, 2001	No, brown sealed envelopes	Unclear, not mentioned	Yes, nothing on swelling	No	Imprecision due to limited sample size (power calculations indicated 400 patients, but due to loss to follow-up only 194 remained)

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/large variability of the results]
Inconsistency	0	
Indirectness	-1	Hospital setting
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Conclusion	There is limited evidence in favour of **no compression**. [In making this evidence conclusion, we place a higher value on the significant outcomes of edema and need for painkillers, which are in favour of no compression over the outcomes of return to work, pain, ankle function and recovery time for which an effect could not be shown.] It was shown that no compression resulted in a statistically significant decrease of edema and pain (need for analgesics), compared to compression (Rucinsky 1991, Watts 2001). However, a statistically significant change of pain improvement, ankle joint function, recovery time or days off work, using compression compared to no compression, could not be demonstrated in 2 other studies (O'Connor 2011, Thorsson 1997). Evidence is of very low quality and results of these studies are imprecise due to limited sample size, lack of data and/or large variability of results.
Reference(s)	**Articles** O'Connor G, Martin AJ. *Acute ankle sprain: is there a best support?* Eur J Emerg Med 2011; 15:225-230 Rucinski TJ, Hooker DN, Prentice WE, Shields EW, Coté-Murray DJ. *The effects of Intermittent Compression on Edema in Postacute Ankle Sprains*. JOSPT 1991; 14(2):65-69. Thorsson O, Lilja B, Nilsson P, Westlin N. *Immediate external compression in the management of an acute muscle injury*. Scand J Med Sci Sports 1997; 7:182-190

	Watts BL, Armstrong B. *A randomized controlled trial to determine the effectiveness of double Tubigrip in grade 1 and 2 (mild to moderate) ankle sprains*. Emerg Med J 2001;18:46-50 **Systematic reviews** van den Bekerom MPJ, Struijs PAA, Blankevoort L, Welling L, van Dijk CN, Kerkhoffs GMMJ. *What is the Evidence for Rest, Ice, Compression, and Elevation Therapy in the Treatment of Ankle Sprains in Adults?* J Athl Train 2012; 47(4):435-443

Strains and sprains – Elevation (First Aid)

Question (PICO)	In humans with strains or sprains (P), is elevation (I) compared to no elevation (C) effective to improve health outcome measures (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Sprains and strains"] OR [mh "Soft Tissue Injuries"] OR "muscle strain":ti,ab,kw OR "ligament sprain*":ti,ab,kw 2. Elevat*:ti,ab,kw OR [mh posture] 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Sprains and strains"[Mesh] OR "Soft Tissue Injuries"[Mesh] OR muscle strain*[TIAB] OR ligament sprain*[TIAB] 2. Elevat*[TIAB] OR "posture"[Mesh] 3. 1-2 AND 4. (((elevat*) AND ((((("ankle injuries"[TIAB] NOT Medline[SB]) OR "ankle injuries"[MeSH Terms] OR ankle injury[Text Word] OR ankle injuries[tw]) OR ("ankle joint"[MeSH Terms] OR ankle joint[Text Word] OR ankle joints[tw]) OR ("lateral ligament, ankle"[MeSH Terms] OR ankle lateral ligament[Text Word] OR ankle lateral ligaments[tw])) OR ((((("sprains and strains"[TIAB] NOT Medline[SB]) OR "sprains and strains"[MeSH Terms] OR sprain[Text Word] OR sprains[tw]) OR (distortion[tw] OR distortions[tw]) OR ("Rupture"[Mesh:noexp] OR rupture[tw] OR ruptures[tw])) AND ("ankle"[MeSH Terms] OR ankle[Text Word] OR ankles[tw]))) AND ((Humans[Mesh]) AND (adult[MeSH])))) AND ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading]) AND ((Humans[Mesh]) AND (adult[MeSH])) 5. 3-4 NOT **Embase** (via Embase.com interface) using the following search strategy: 1. 'sprain'/exp OR 'ligament injury'/exp OR 'soft tissue injury'/exp OR 'muscle strain':ab,ti OR 'ligament sprain':ab,ti 1.'term1'/exp OR 'term2'/exp OR 'term3'/exp OR 'text word' 2. Elevat*:ab,ti OR 'body posture'/exp 3. 1-2 AND **Cinahl** 1. (MH "Sprains and Strains+") OR (MH "Soft Tissue Injuries+") OR TI "muscle strain*" OR AB "muscle strain*" OR TI ligament sprain* OR AB ligament sprain* 2. TI Elevat* OR AB elevat* OR (MH "Posture+") 3. 1-2 AND Guidelines, systematic reviews, retrieved with the above searches, and used as source for individual studies:

	van den Bekerom, 2012
Search date	5 November 2014
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: functional recovery, pain, swelling, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies. **Language**: Include: English **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	**Systematic reviews** van den Bekerom MPJ, Struijs PAA, Blankevoort L, Welling L, van Dijk CN, Kerkhoffs GMMJ. *What is the Evidence for Rest, Ice, Compression, and Elevation Therapy in the Treatment of Ankle Sprains in Adults?* J Athl Train 2012; 47(4):435-443

Sprains and strains – Cooling gels or sprays (First Aid)

Question (PICO)	In humans with sprains or strains (P), is the use of a cooling gel (I) compared to not using this (C) effective to improve health outcome measures (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh ointments] OR [mh emollients] OR salve*:ti,ab,kw OR ointment*:ti,ab,kw OR unguent*:ti,ab,kw OR paste*:ti,ab,kw OR spray*:ti,ab,kw OR lotion*:ti,ab,kw OR cream*:ti,ab,kw OR gel:ti,ab,kw OR gels:ti,ab,kw

	2. [mh “Sprains and strains”] OR [mh "Soft Tissue Injuries"] OR “muscle strain*”:ti,ab,kw OR “ligament sprain*”:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. ointments[Mesh] OR emollients[Mesh] OR salve*[TIAB] OR ointment*[TIAB] OR unguent*[TIAB] OR paste*[TIAB] OR spray*[TIAB] OR lotion*[TIAB] OR cream*[TIAB] OR gel[TIAB] OR gels[TIAB] 2. “Sprains and strains”[Mesh] OR "Soft Tissue Injuries"[Mesh] OR “muscle strain*”[TIAB] OR “ligament sprain*”[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. ointment/exp OR ‘emollient agent’/exp OR salve/exp OR ointment*:ab,ti OR salve*:ab,ti OR unguent*:ab,ti OR paste*:ab,ti OR spray*:ab,ti OR lotion*:ab,ti OR cream*:ab,ti OR gel:ab,ti OR gels:ab,ti 2. ‘sprain’/exp OR 'ligament injury'/exp OR 'soft tissue injury'/exp OR 'muscle strain':ab,ti OR ‘ligament sprain’:ab,ti 3. 1-2 AND <u>In each database, an extra search was performed to look for studies on specific products:</u> **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. cool*:ti,ab,kw 2. [mh ointments] OR [mh emollients] OR salve*:ti,ab,kw OR ointment*:ti,ab,kw OR unguent*:ti,ab,kw OR paste*:ti,ab,kw OR spray*:ti,ab,kw OR lotion*:ti,ab,kw OR cream*:ti,ab,kw OR gel:ti,ab,kw OR gels:ti,ab,kw 3. reflex:ti,ab,kw OR flexium:ti,ab,kw OR fastum:ti,ab,kw OR voltaren:ti,ab,kw OR "ice power":ti,ab,kw OR Spiroflor:ti,ab,kw OR Alaska:ti,ab,kw OR Arnica:ti,ab,kw 4. 1-3 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. cool*[TIAB] 2. ointments[Mesh] OR emollients[Mesh] OR salve*[TIAB] OR ointment*[TIAB] OR unguent*[TIAB] OR paste*[TIAB] OR spray*[TIAB] OR lotion*[TIAB] OR cream*[TIAB] OR gel[TIAB] OR gels[TIAB] 3. reflex[TIAB] OR flexium[TIAB] OR fastum[TIAB] OR voltaren[TIAB] OR Spiroflor[TIAB] OR Alaska[TIAB] OR Arnica[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Cool*:ab,ti 2. ointment/exp OR ‘emollient agent’/exp OR salve/exp OR ointment*:ab,ti OR salve*:ab,ti OR unguent*:ab,ti OR paste*:ab,ti OR spray*:ab,ti OR lotion*:ab,ti OR cream*:ab,ti OR gel:ab,ti OR gels:ab,ti 3. reflex:ab,ti OR flexium:ab,ti OR fastum:ab,ti OR voltaren:ab,ti OR ‘ice power’:ab,ti OR Spiroflor:ab,ti OR Alaska:ab,ti OR Arnica:ab,ti 4. 1-3 AND <u>Included articles, retrieved with the above searches</u>, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	25 November 2015
In/Exclusion criteria	**Population**: <u>Include</u>: People with sprains and strains

	Intervention: Include: cooling gels or sprays. We included only studies that specifically mentioned the gel or spray has a (possibly) cooling effect. Exclude: gels or sprays of which it is not mentioned they (might) have a cooling effect. **Comparison**: Include: no cooling gels/sprays or placebo gels/sprays. Exclude: comparison to other gels/sprays, oral treatments. **Outcome:** Include: cooling, functional recovery, pain, swelling, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Airaksinen, 2003, Finland	Experimental: Randomized controlled trial	74 patients with sports related soft tissue injury of the ankle, leg, knee or hand. Patients were randomized to active cold gel (13 women, 24 men, mean age 32±12 years) or placebo (14 women, 23 men, mean age 32±10 years). Only patients with minor soft tissue injury of the extremities that had occurred less than 48 h before the examination were included.	1. Active cold gel (Ice Power, 3.5% menthol + 8% ethanol + adjuvants): 5 g of gel 4x/day for 14 days. 2. Placebo (similar to cold gel, but without menthol and ethanol): same treatment with placebo gel.	Patients were allowed to use nonsteroidal anti-inflammatory drugs as a rescue medication. Any use was recorded. Patients with knee or ankle injuries used elastic bandages for 14 days.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Pain at rest (VAS, mm)	Active cold gel vs placebo	Statistically significant: day 7: 30±16 vs 45±15 MD: -15.0, 95%CI [-22.07; -7.93] (p<0.0001)* *In favour of active cold gel* day 14: 14±13 vs 26±18	1, 37 vs 37 §	Airaksinen, 2003

		MD: -12.0, 95%CI [-19.15; -4.85] (p<0.001)* *In favour of active cold gel* day 28: 7±12 vs 13±14 MD: -6.0, 95%CI [-11.94; -0.06] (p<0.05)* *In favour of active cold gel*		
Pain at movement (VAS, mm)		<u>Statistically significant</u>: day 7: 27±13 vs 41±14 MD: -14.0, 95%CI [-20.16; -7.84] (p<0.00001)* *In favour of active cold gel* day 14: 13±12 vs 21±13 MD: -8.0, 95%CI [-13.70; -2.30] (p=0.006)* *In favour of active cold gel* day 28: 6±12 vs 13±12 MD: -7.0, 95%CI [-12.47; -1.53] (p=0.01)* *In favour of active cold gel*		
Functional disability (VAS, mm)		<u>Statistically significant</u>: day 7: 32±20 vs 45±19 MD: -13.0, 95%CI [-21.89; -4.11] (p=0.004)*λ *In favour of active cold gel* day 14: 19±13 vs 26±17 MD: -7.0, 95%CI [-13.90; -0.10] (p<0.05)*λ *In favour of active cold gel* day 28: 7.5±5.6 vs 13±13 MD: -5.5, 95%CI [-10.06; -0.94] (p=0.02)*λ *In favour of active cold gel*		

Mean ± SD

* Calculations done by the reviewer(s) using Review Manager software

§ Imprecision (limited sample size)

λ Data extracted from graph

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Airaksinen, 2003	No, randomization by computer	No, double-blinded	No	No	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Moderate [B]**	

Conclusion	There is limited evidence in favour of cold gel. It was shown that active cold gel resulted in a statistically significant decrease of pain at rest, pain at movement and functional disability, compared to placebo (Airaksinen 2003). Evidence is of moderate quality and results cannot be considered precise due to limited sample size.
Reference(s)	**Articles** Airaksinen OV, Kyrklund Nils, Latvala K, Kouri JP, Grönblad M, Kolari P. *Efficacy of Cold Gel for Soft Tissue Injuries. A Prospective Randomized Double-Blinded Trial*. Am J Sports Med 2003, 31(5):680-684

Sprains and strains – Compression/elastic bandage (Prevention)

Question (PICO)	In humans (P), is using a compression/elastic bandage (I), compared to not using a compression/elastic bandage (C), effective as a prevention technique for sprains (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Sprains and strains"] OR [mh "Soft Tissue Injuries"] OR "muscle strain":ti,ab,kw OR "ligament sprain*":ti,ab,kw 2. [mh "Compression Bandages"] OR ((compression:ti,ab,kw OR elastic:ti,ab,kw) AND bandag*:ti,ab,kw) 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Sprains and strains"[Mesh] OR "Soft Tissue Injuries"[Mesh] OR muscle strain*[TIAB] OR ligament sprain*[TIAB] 2. "Compression Bandages"[Mesh] OR ((compression [TIAB] OR elastic[TIAB]) AND bandag*[TIAB]) 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'sprain'/exp OR 'ligament injury'/exp OR 'soft tissue injury'/exp OR 'muscle strain':ab,ti OR 'ligament sprain':ab,ti 2. 'compression bandage'/exp OR ((compression:ab,ti OR elastic:ab,ti) AND bandag*:ab,ti) 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	5 November 2014
In/Exclusion criteria	**Population**: Include: healthy volunteers of all ages. **Intervention**: Include: compression/elastic bandaging Exclude: bracing, taping

	Outcome: Include: Direct sprain/strain-related outcomes (e.g. pain). (Indirect) biomechanical outcomes were only included if direct sprain/strain-related outcomes were absent. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Trégouët, 2013, France	Experimental: randomized controlled trial (within subjects design)	12 healthy volunteers (24.1±6.8 years were tested on an inversion platform in the following taping conditions: elastic adhesive bandage wrap (intervention) and non-taped control (control)	Intervention: elastic adhesive bandaging (adhesive spray; pre-wrap; 2.5 cm zinc oxide anchors; stirrups; start and finish medially 2.5 cm zinc oxide; Figure-of-8; close, continuous, with 7.5cm elastic adhesive bandage) Control: non-taped condition	Testing was done before and after 30 minutes of treadmill running

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Total inversion of the ankle (°)	Elastic bandaging vs no bandaging	Statistically significant: 26±5 vs 33±7 MD: -7 £ (p<0.05) *In favour of elastic bandaging*	1, 12 vs 12 (within subjects design) §	Trégouët, 2013
Rate of ankle inversion (°/sec)		Statistically significant: 248±73 vs 339±109 MD: -91 £ (p<0.05) *In favour of elastic bandaging*		

Mean±SD (unless stated otherwise)

£ CI cannot be calculated

§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Trégouët, 2013	No	No	No	No	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Limited sample size
Inconsistency	0	
Indirectness	-1	Biomechanical outcomes, no sprain-related outcomes (e.g. pain)
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is limited evidence in favour of elastic bandaging**.** It was shown that elastic bandaging resulted in a statistically significant decreased (rate of) total ankle inversion compared to no elastic bandaging (Trégouët 2013). Evidence is of low quality and results of this study are imprecise due to limited sample size.
Reference(s)	**Articles** Trégouët P, Merland F, Horodyski MB. *A comparison of the effects of ankle taping styles on biomechanics during ankle inversion*. Ann Phys Rehabil Med. 2013;56(2):113-122.

Muscle cramps – Stretching exercises (First Aid/Prevention)

Question (PICO)	In humans (P), are stretching exercises (I) effective as treatment or prevention of (exercise-associated) muscle cramps (O) compared to no stretching exercises (C)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "muscle cramp"] OR [mh "musculoskeletal pain"] OR [mh "athletic injuries"] OR cramp:ti,ab,kw OR cramps:ti,ab,kw OR "delayed onset muscle soreness":ti,ab,kw OR "delayed onset muscular soreness":ti,ab,kw 2. [mh "muscle stretching exercises"] OR stretching:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for systematic reviews, experimental and observational studies using the following search strategy: 1. "muscle cramp"[Mesh] OR "musculoskeletal pain"[Mesh] OR "athletic injuries"[Mesh] OR cramp[TIAB] OR cramps[TIAB] OR "delayed onset muscle soreness"[TIAB] OR "delayed onset muscular soreness"[TIAB] 2. "muscle stretching exercises"[Mesh] OR stretching[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) for systematic reviews, experimental and observational studies using the following search strategy: 1. 'muscle cramp'/exp OR 'musculoskeletal pain'/exp OR 'sport injury'/exp OR cramp:ab,ti OR cramps:ab,ti OR 'delayed onset muscle soreness':ab,ti OR 'delayed onset muscular soreness':ab,ti 2. 'stretching exercise'/exp OR stretching:ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	09 September 2015
In/Exclusion criteria	**Population**: Include: Humans with (exercise-associated) muscle cramps. **Intervention**: Include: (active or passive) stretching exercises as prevention or as first aid technique.

	Comparison: Include: no/placebo stretching exercises **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies.

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Blyton, 2012, Australia	(Cochrane) Systematic review	1 randomized controlled trial with 97 participants (≥ 60 years of age) having night time cramps and completed lean-to-wall calf muscle stretching (intervention, n=49) or placebo stretching (control, n=48)	Intervention: calf muscle stretching exercises (held for 10s three times per day during 6 weeks) Control: placebo stretching (passive non-stretching exercises, held for 10s three times per day during 6 weeks)	
Herbert, 2011, Australia	(Cochrane) Systematic review	12 (quasi-) randomized controlled trials including 2377 participants, 1220 of whom were allocated stretching. All other 11 studies were small, with between 10 and 30 participants receiving the stretch condition (intervention).	Intervention: Any pre-exercise or post-exercise stretching technique (conducted soon before/after exercise of any type) Control: no stretching	Cochrane review last assessed as up-to-date: 7 May 2010

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Pre-exercise stretching				
Muscle soreness (pain) on day 1 (18-30 hours post-exercise)	Pre-exercise stretching vs no stretching	Not statistically significant: MD: -0.52, 95%CI [-11.30; 10.26] (p=0.92) £†	3, 34 vs 36 §	Herbert, 2011
Muscle soreness (pain) on day 2 (42-54 hours post-exercise)		Not statistically significant: MD: 0.72, 95%CI [-11.20; 12.64] (p=0.91) £†	2, 20 vs 20 §	
Muscle soreness (pain) on day 3 (66-78 hours post-exercise)		Not statistically significant: MD: -2.50, 95%CI [-15.82; 10.82] (p=0.71) £†	2, 20 vs 20 §	
Post-exercise stretching				

Muscle soreness (pain) on day 1 (18-30 hours post-exercise)	Post-exercise stretching vs no stretching	Not statistically significant: MD: -1.04, 95%CI [-6.88;4.79] (p=0.73) £†	4, 67 vs 60 §	Herbert, 2011
Muscle soreness (pain) on day 2 (42-54 hours post-exercise)		Not statistically significant: MD: 1.12, 95%CI [-4.63;6.87] (p=0.70) £†	5, 81 vs 77 §	
Muscle soreness (pain) on day 3 (66-78 hours post-exercise)		Not statistically significant: MD: -0.03, 95%CI [-7.49;7.43] (p=0.99) £†	3, 37 vs 30 §	
Either pre-exercise or post-exercise stretching				
Muscle soreness (pain) on day 1 (18-30 hours post-exercise)	Pre- or post-exercise stretching vs no stretching	Not statistically significant: MD: -0.93, 95%CI [-6.05;4.20] (p=0.72) £†	7, 101 vs 96 §	Herbert, 2011
Muscle soreness (pain) on day 2 (42-54 hours post-exercise)		Not statistically significant: MD: 1.04, 95%CI [-4.14;6.22] (p=0.69) £†	7, 101 vs 97 §	
Muscle soreness (pain) on day 3 (66-78 hours post-exercise)		Not statistically significant: MD: -0.28, 95%CI [-6.79;6.22] (p=0.93) £†	5, 57 vs 50 §	
Both pre-exercise and post-exercise stretching				
Muscle soreness (pain) in preceding week	Pre- and post-exercise stretching vs no stretching	Statistically significant: MD: -3.80, 95%CI [-5.17;-2.43] (p<0.00001) £ *In favour of pre- and post-exercise stretching*	1, 1190 vs 1133	Herbert, 2011
Bothersome soreness		Statistically significant: OR: 0.69, 95%CI [0.59;0.82] (p=0.000015) ££ *In favour of pre- and post-exercise stretching*		
Non-exercise related stretching				
Number of (nighttime) lower limb muscle cramps in the last 4 weeks	Calf muscle stretching versus placebo stretching	Not statistically significant: 10.02±17.67 vs 8.83±17.234, MD: 1.19, 95%CI [-5.86;8.25] (p<0.00001) ¥	1, 48 vs 46 §	Blyton, 2012

Data are presented as means±SD
§ Imprecision (limited sample size)
£ No raw data and SD's available
££ No raw data available
† Imprecision (lack of data)
¥ Imprecision (large variability of results)

Level of evidence
(Either) Pre-exercise or post-exercise stretching

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See systematic review Herbert 2011
Imprecision	-1	Limited sample size and lack of data
Inconsistency	0	
Indirectness	-1	Soreness as indirect outcome for muscle cramps
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Pre-exercise and post-exercise stretching

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See systematic review Herbert 2011
Imprecision	0	
Inconsistency	0	
Indirectness	-1	Soreness as indirect outcome for muscle cramps
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Non-exercise related stretching

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See systematic review Herbert 2011
Imprecision	-1	Limited sample size and large variability in results
Inconsistency	0	
Indirectness	-1	Soreness as indirect outcome for muscle cramps
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Conclusion	**(Either) Pre-exercise or post-exercise stretching** There is limited evidence neither in favour of (either) pre-exercise or post-exercise stretching nor no stretching. A statistically significant reduced muscle soreness, using (either) pre-exercise or post-exercise stretching compared to no stretching, could not be demonstrated (Herbert 2011). Evidence is of very low quality and results are imprecise due to limited sample size. **Pre-exercise and post-exercise stretching** There is limited evidence in favour of performing both pre- and post-exercise stretching. It was shown that pre- and post-exercise stretching resulted in a statistically significant reduced muscle soreness, compared to no stretching (Herbert 2011). Evidence is of low quality. **Non-exercise related stretching** There is limited evidence neither in favour of stretching nor placebo stretching. A statistically significant reduced number of (nighttime) muscle cramps, using stretching exercises compared to placebo stretching, could not be demonstrated (Blyton 2012). Evidence is of very low quality and results are imprecise due to limited sample size.
Reference(s)	**Systematic reviews** Blyton F, Chuter V, Walter KE, Burns J. *Non-drug therapies for lower limb muscle cramps.* Cochrane Database Syst Rev. 2012, 18;1:CD008496. Herbert RD, de Noronha M, Kamper SJ. *Stretching to prevent or reduce muscle soreness after exercise*. Cochrane Database Syst Rev. (7):CD004577.

Muscle cramps – Massage (First Aid)

Question (PICO)	In humans (P), is massage (I) effective as treatment of muscle cramps (O) compared to no massage (C)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy:

	1. [mh "muscle cramp"] OR [mh "musculoskeletal pain"] OR [mh "athletic injuries"] OR cramp:ti,ab,kw OR cramps:ti,ab,kw OR "delayed onset muscle soreness":ti,ab,kw OR "delayed onset muscular soreness":ti,ab,kw 2. [mh massage] OR massage:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for systematic reviews, experimental and observational studies using the following search strategy: 1. "muscle cramp"[Mesh] OR "musculoskeletal pain"[Mesh] OR "athletic injuries"[Mesh] OR cramp[TIAB] OR cramps[TIAB] OR "delayed onset muscle soreness"[TIAB] OR "delayed onset muscular soreness"[TIAB] 2. "massage"[Mesh] OR massage[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) for systematic reviews, experimental and observational studies using the following search strategy: 1. 'muscle cramp'/exp OR 'musculoskeletal pain'/exp OR 'sport injury'/exp OR cramp:ab,ti OR cramps:ab,ti OR 'delayed onset muscle soreness':ab,ti OR 'delayed onset muscular soreness':ab,ti 2. massage/exp OR massage:ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	11 September 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: massage **Comparison**: Include: no intervention **Outcome**: Include: health-related outcomes of muscle cramps, soreness, pain **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies.

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Andersen, 2013, Denmark	Experimental: randomized controlled trial (within subjects design)	20 healthy female volunteers (mean age 32 years) performed eccentric contractions for the upper trapezius muscle	Intervention: 10 minutes of massage of the trapezius muscle (after 48 h) Control: no massage	Power calculations performed before the study showed that 20 participants in a paired design were necessary for testing the null hypothesis of equality of treatment at an alpha level of 5%, a statistical power of 80%, an SD of 1.5 and a minimally relevant difference in the intensity of soreness of 1 on a scale of 0–10

Jay, 2014, Denmark	Experimental: randomized controlled trial	22 healthy untrained men (mean age 34±7 years performed 10 x 10 repetitions of the stiff-legged dead-lift 48 hours later one group (n=11, 35±8 years) received 10 minutes of roller massage on one leg (intervention) while the other group received no massage (n=11, 33±7 years)	Intervention: 10 minutes of roller massage Control: no massage	Power calculations performed prior to the study showed that 10 participants in each group in an unpaired design (i.e. massage vs. control group) were necessary for testing the null hypothesis of equality of treatment at an alpha level of 5%, a statistical power of 80%, a standard deviation of 1.5 and a minimally relevant difference in intensity of soreness of 2 on a scale of 0-10. Finally, an expected cross over effect from the massage to the contralateral leg of 1.5 with a SD of 1.5, given a power of 80% in a paired design was estimated.
Torres, 2012, Portugal	Systematic review	9 randomized controlled trials on adults (18-60 years) of both gender that included massage as a physiotherapeutic intervention as a possible effective intervention for treating signs and symptoms of exercise-induced muscle damage	Intervention: massage Control: no massage	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Massage immediately after exercise				
Muscle soreness (VAS 0-10) at 1 hour post-exercise	Massage vs no massage	Not statistically significant: MD: -0.11, 95%CI [-0.39;0.18] (p=0.46) £†	2, 14 vs 14 §	Torres, 2012
Muscle soreness (VAS 0-10) at 24 hours post-exercise		Statistically significant: MD: -0.33, 95%CI [-0.59;-0.07] (p=0.01) £ *In favour of massage*	4, 30 vs 30 §	
Muscle soreness (VAS 0-10) at 48 hours post-exercise		Not statistically significant: MD: -0.96, 95%CI [-2.02;0.09] (p=0.07) £†	3, 22 vs 22 §	
Muscle soreness (VAS 0-10) at 72 hours post-exercise		Not statistically significant: MD: 0.28, 95%CI [-0.01;0.58] (p=0.06) £†	3, 25 vs 25 §	
Massage 48 hours after exercise				

Muscle soreness (VAS 0-10) 10 minutes after treatment	Massage vs no massage	Statistically significant: MD: -0.7, 95%CI [-0.3;-1.1] (p<0.05) £ *In favour of massage*	1, 20 vs 20 (power analysis)	Andersen, 2013
		Statistically significant: MD: -2.23, 95%CI [-1.40;-3.06] (p<0.05) £ *In favour of massage*	1, 11 vs 11 (power analysis)	Jay, 2014
Muscle soreness (VAS 0-10) 20 minutes after treatment		Statistically significant: MD: -0.5, 95%CI [-0.1;-0.9] (p<0.05) £ *In favour of massage*	1, 20 vs 20 (power analysis)	Andersen, 2013
Muscle soreness (VAS 0-10) 30 minutes after treatment		Statistically significant: MD: -1.82, 95%CI [-0.99;-2.65] (p<0.05) £ *In favour of massage*	1, 11 vs 11 (power analysis)	Jay, 2014
Muscle soreness (VAS 0-10) 60 minutes after treatment		Not statistically significant: MD: -0.3, 95%CI [0.1;-0.7] (p<0.05) £†	1, 20 vs 20 (power analysis)	Andersen, 2013
		Statistically significant: MD: -1.78, 95%CI [-0.94;-2.61] (p<0.05) £ *In favour of massage*	1, 11 vs 11 (power analysis)	Jay, 2014

§ Imprecision (limited sample size)
£ No raw data and SD's available
† Imprecision (lack of data)

Massage immediately after exercise
Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See systematic review Torres 2012
Imprecision	-1	Limited sample size and/or lack of data
Inconsistency	0	
Indirectness	-1	Soreness as indirect outcome for muscle cramps
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [C]**	

Massage 48 hours after exercise
Quality of evidence

Author, Year	**Lack of allocation concealment**	**Lack of blinding**	**Incomplete accounting of outcome events**	**Selective outcome reporting**	**Other limitations**
Andersen, 2013	No	No	No	No	Within-subjects design
Jay, 2014	Unclear	No	No	No	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See 'Quality of evidence' table
Imprecision	0	
Inconsistency	0	
Indirectness	-1	Soreness as indirect outcome for muscle cramps
Publication bias	0	
QUALITY (GRADE)	**Final grading Moderate[B]**	

Conclusion	**Massage immediately after exercise** There is limited evidence in favour of massage. It was shown that massage resulted in a statistically significant reduced muscle soreness 24 hours after exercise, compared to no massage (Torres 2012). However, a statistically significant reduced muscle soreness 1 hour/2 days/3 days after exercise, using massage compared to no massage, could not be demonstrated (Torres 2012). Evidence is of moderate quality. **Massage 48 hours after exercise** There is limited evidence in favour of massage. It was shown that massage resulted in a statistically significant reduced muscle soreness 10-60 minutes after massage, compared to no massage (Andersen 2013 and Jay 2014). However, a statistically significant reduced muscle soreness 60 minutes after massage, compared to no massage, could not be demonstrated on one study (Andersen 2013). Evidence is of low quality and results cannot be considered precise due to the lack of data.
Reference(s)	**Articles** Andersen LL, Jay K, Andersen CH, Jakobsen MD, Sundstrup E, Topp R, Behm DG. *Acute effects of massage or active exercise in relieving muscle soreness: randomized controlled trial*. J Strength Cond Res. 2013, 27(12):3352-3359. Jay K, Sundstrup E, Søndergaard SD[1], Behm D[2], Brandt M[1], Særvoll CA[1], Jakobsen MD[1], Andersen LL[1]. *Specific and cross over effects of massage for muscle soreness: randomized controlled trial*. Int J Sports Phys Ther. 2014, 9(1):82-91. **Systematic reviews** Torres R, Ribeiro F, Alberto Duarte J, Cabri JM. *Evidence of the physiotherapeutic interventions used currently after exercise-induced muscle damage: systematic review and meta-analysis.* Phys Ther Sport. 2012, 13(2):101-114.

Muscle cramps – Massage/heat application (after exercise in hot environment) (First Aid)

Question (PICO)	In humans performing exercise in a hot environment (P), is massage/heat application (I) effective as treatment of exercise-associated muscle cramps (O) compared to no massage/heat application (C)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "muscle cramp"] OR [mh "musculoskeletal pain"] OR [mh "athletic injuries"] OR cramp:ti,ab,kw OR cramps:ti,ab,kw OR "delayed onset muscle soreness":ti,ab,kw OR "delayed onset muscular soreness":ti,ab,kw 2. [mh "hot temperature"] OR [mh massage] OR massage:ti,ab,kw OR heat:ti,ab,kw 3. ((hot:ti,ab,kw OR warm:ti,ab,kw) AND (temperature:ti,ab,kw OR environment:ti,ab,kw OR weather:ti,ab,kw OR condition:ti,ab,kw)) 4. 1-3 AND **MEDLINE** (via PubMed interface) for systematic reviews, experimental and observational studies using the following search strategy: 1. "muscle cramp"[Mesh] OR "musculoskeletal pain"[mesh] OR "athletic injuries"[Mesh] OR "cramp"[TIAB] OR "cramps"[TIAB] OR "delayed onset muscle soreness"[TIAB] OR "delayed onset muscular soreness"[TIAB] 2. "hot temperature"[Mesh] OR massage[Mesh] OR massage[TIAB] OR heat[TIAB] 3. ((hot[TIAB] OR warm[TIAB]) AND (temperature[TIAB] OR environment[TIAB] OR weather[TIAB] OR condition[TIAB])) 4. 1-3 AND

	Embase (via Embase.com interface) for systematic reviews, experimental and observational studies using the following search strategy: 1. 'muscle cramp'/exp OR 'musculoskeletal pain'/exp OR 'sport injury'/exp OR cramp:ab,ti OR cramps:ab,ti OR 'delayed onset muscle soreness':ab,ti OR 'delayed onset muscular soreness':ab,ti 2. heat/exp OR massage/exp OR heat:ab,ti OR massage:ab,ti 3. ((hot:ab,ti OR warm:ab,ti) AND (temperature:ab,ti OR environment:ab,ti OR weather:ab,ti OR condition:ab,ti)) 4. 1-3 AND
Search date	09 September 2015
In/Exclusion criteria	**Population**: Include: people of all ages that performed any exercise in a hot environment. **Intervention**: Include: heat application/massage **Comparison:** Include: no heat application/massage **Outcome**: Include: (in-)direct outcomes related to muscle cramps **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies.

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Muscle cramps – Stretching exercises (First Aid/Prevention)

Question (PICO)	In humans (P), are stretching exercises (I) effective as treatment or prevention of (exercise-associated) muscle cramps (O) compared to no stretching exercises (C)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "muscle cramp"] OR [mh "musculoskeletal pain"] OR [mh "athletic injuries"] OR cramp:ti,ab,kw OR cramps:ti,ab,kw OR "delayed onset muscle soreness":ti,ab,kw OR "delayed onset muscular soreness":ti,ab,kw 2. [mh "muscle stretching exercises"] OR stretching:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for systematic reviews, experimental and observational studies using the following search strategy: 1. "muscle cramp"[Mesh] OR "musculoskeletal pain"[Mesh] OR "athletic injuries"[Mesh] OR cramp[TIAB] OR cramps[TIAB] OR "delayed onset muscle soreness"[TIAB] OR "delayed onset muscular soreness"[TIAB]

	2. "muscle stretching exercises"[Mesh] OR stretching[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) for systematic reviews, experimental and observational studies using the following search strategy: 1. 'muscle cramp'/exp OR 'musculoskeletal pain'/exp OR 'sport injury'/exp OR cramp:ab,ti OR cramps:ab,ti OR 'delayed onset muscle soreness':ab,ti OR 'delayed onset muscular soreness':ab,ti 2. 'stretching exercise'/exp OR stretching:ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	09 September 2015
In/Exclusion criteria	**Population**: Include: Humans with (exercise-associated) muscle cramps. **Intervention**: Include: (active or passive) stretching exercises as prevention or as first aid technique. **Comparison**: Include: no/placebo stretching exercises **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies.

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Blyton, 2012, Australia	(Cochrane) Systematic review	1 randomized controlled trial with 97 participants (≥ 60 years of age) having night time cramps and completed lean-to-wall calf muscle stretching (intervention, n=49) or placebo stretching (control, n=48)	Intervention: calf muscle stretching exercises (held for 10s three times per day during 6 weeks) Control: placebo stretching (passive non-stretching exercises, held for 10s three times per day during 6 weeks)	
Herbert, 2011, Australia	(Cochrane) Systematic review	12 (quasi-) randomized controlled trials including 2377 participants, 1220 of whom were allocated stretching. All other 11 studies were small, with between 10 and 30 participants receiving the stretch condition (intervention).	Intervention: Any pre-exercise or post-exercise stretching technique (conducted soon before/after exercise of any type) Control: no stretching	Cochrane review last assessed as up-to-date: 7 May 2010

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Pre-exercise stretching				
Muscle soreness (pain) on day 1 (18-30 hours post-exercise)	Pre-exercise stretching vs no stretching	Not statistically significant: MD: -0.52, 95%CI [-11.30; 10.26] (p=0.92) £†	3, 34 vs 36 §	Herbert, 2011
Muscle soreness (pain) on day 2 (42-54 hours post-exercise)		Not statistically significant: MD: 0.72, 95%CI [-11.20; 12.64] (p=0.91) £†	2, 20 vs 20 §	
Muscle soreness (pain) on day 3 (66-78 hours post-exercise)		Not statistically significant: MD: -2.50, 95%CI [-15.82; 10.82] (p=0.71) £†	2, 20 vs 20 §	
Post-exercise stretching				
Muscle soreness (pain) on day 1 (18-30 hours post-exercise)	Post-exercise stretching vs no stretching	Not statistically significant: MD: -1.04, 95%CI [-6.88;4.79] (p=0.73) £†	4, 67 vs 60 §	Herbert, 2011
Muscle soreness (pain) on day 2 (42-54 hours post-exercise)		Not statistically significant: MD: 1.12, 95%CI [-4.63;6.87] (p=0.70) £†	5, 81 vs 77 §	
Muscle soreness (pain) on day 3 (66-78 hours post-exercise)		Not statistically significant: MD: -0.03, 95%CI [-7.49;7.43] (p=0.99) £†	3, 37 vs 30 §	
Either pre-exercise or post-exercise stretching				
Muscle soreness (pain) on day 1 (18-30 hours post-exercise)	Pre- or post-exercise stretching vs no stretching	Not statistically significant: MD: -0.93, 95%CI [-6.05;4.20] (p=0.72) £†	7, 101 vs 96 §	Herbert, 2011
Muscle soreness (pain) on day 2 (42-54 hours post-exercise)		Not statistically significant: MD: 1.04, 95%CI [-4.14;6.22] (p=0.69) £†	7, 101 vs 97 §	
Muscle soreness (pain) on day 3 (66-78 hours post-exercise)		Not statistically significant: MD: -0.28, 95%CI [-6.79;6.22] (p=0.93) £†	5, 57 vs 50 §	
Both pre-exercise and post-exercise stretching				
Muscle soreness (pain) in preceding week	Pre- and post-exercise stretching vs no stretching	Statistically significant: MD: -3.80, 95%CI [-5.17;-2.43] (p<0.00001) £ *In favour of pre- and post-exercise stretching*	1, 1190 vs 1133	Herbert, 2011
Bothersome soreness		Statistically significant: OR: 0.69, 95%CI [0.59;0.82] (p=0.000015) ££ *In favour of pre- and post-exercise stretching*		
Non-exercise related stretching				
Number of (nighttime) lower	Calf muscle stretching versus placebo stretching	Not statistically significant: 10.02±17.67 vs 8.83±17.234, MD:	1, 48 vs 46 §	Blyton, 2012

limb muscle cramps in the last 4 weeks		1.19, 95%CI [-5.86;8.25] (p<0.00001) ¥		

Data are presented as means±SD
§ Imprecision (limited sample size)
£ No raw data and SD's available
££ No raw data available
† Imprecision (lack of data)
¥ Imprecision (large variability of results)

Level of evidence

(Either) Pre-exercise or post-exercise stretching

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See systematic review Herbert 2011
Imprecision	-1	Limited sample size and lack of data
Inconsistency	0	
Indirectness	-1	Soreness as indirect outcome for muscle cramps
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Pre-exercise and post-exercise stretching

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See systematic review Herbert 2011
Imprecision	0	
Inconsistency	0	
Indirectness	-1	Soreness as indirect outcome for muscle cramps
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Non-exercise related stretching

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See systematic review Herbert 2011
Imprecision	-1	Limited sample size and large variability in results
Inconsistency	0	
Indirectness	-1	Soreness as indirect outcome for muscle cramps
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Conclusion	**(Either) Pre-exercise or post-exercise stretching** There is limited evidence neither in favour of (either) pre-exercise or post-exercise stretching nor no stretching. A statistically significant reduced muscle soreness, using (either) pre-exercise or post-exercise stretching compared to no stretching, could not be demonstrated (Herbert 2011). Evidence is of very low quality and results are imprecise due to limited sample size. **Pre-exercise and post-exercise stretching**

	There is limited evidence in favour of performing both pre- and post-exercise stretching. It was shown that pre- and post-exercise stretching resulted in a statistically significant reduced muscle soreness, compared to no stretching (Herbert 2011). Evidence is of low quality. **Non-exercise related stretching** There is limited evidence neither in favour of stretching nor placebo stretching. A statistically significant reduced number of (nighttime) muscle cramps, using stretching exercises compared to placebo stretching, could not be demonstrated (Blyton 2012). Evidence is of very low quality and results are imprecise due to limited sample size.
Reference(s)	**Systematic reviews** Blyton F, Chuter V, Walter KE, Burns J. *Non-drug therapies for lower limb muscle cramps.* Cochrane Database Syst Rev. 2012, 18;1:CD008496. Herbert RD, de Noronha M, Kamper SJ. *Stretching to prevent or reduce muscle soreness after exercise*. Cochrane Database Syst Rev. (7):CD004577.

Muscle cramps – Cooling-down (Prevention)

Question (PICO)	In people (P), is cooling down after exercise (I) effective as prevention of muscle cramps (O) compared to no cooling down after exercise (C)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "muscle cramp"] OR [mh "musculoskeletal pain"] OR [mh "athletic injuries"] OR cramp:ti,ab,kw OR cramps:ti,ab,kw OR "delayed onset muscle soreness":ti,ab,kw OR "delayed onset muscular soreness":ti,ab,kw 2. (("cool down":ti,ab,kw OR "cool-down":ti,ab,kw OR cooldown:ti,ab,kw) AND (exercise*)) 3. 1-2 AND **MEDLINE** (via PubMed interface) for systematic reviews, experimental and observational studies using the following search strategy: 1. "muscle cramp"[Mesh] OR "musculoskeletal pain"[Mesh] OR "athletic injuries"[Mesh] OR cramp[TIAB] OR cramps[TIAB] OR "delayed onset muscle soreness"[TIAB] OR "delayed onset muscular soreness"[TIAB] 2. "cool-down exercise"[Mesh] OR (("cool down"[TIAB] OR "cool-down"[TIAB] OR cooldown[TIAB]) AND (exercise*)) 3. 1-2 AND **Embase** (via Embase.com interface) for systematic reviews, experimental and observational studies using the following search strategy: 1. 'muscle cramp'/exp OR 'musculoskeletal pain'/exp OR 'sport injury'/exp OR cramp:ab,ti OR cramps:ab,ti OR 'delayed onset muscle soreness':ab,ti OR 'delayed onset muscular soreness':ab,ti 2. 'cool down'/exp OR (('cool down':ab,ti OR 'cool-down':ab,ti OR cooldown:ab,ti) AND (exercise*)) 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	10 September 2015
In/Exclusion criteria	**Population**: Include: Humans with exercise-associated muscle cramps.

	Intervention: Include: (active or passive) cool-down exercises (after exercise). Cooling-down is defined as easy exercises (i.e. at (very) low intensities) that will allow the body to gradually transition to a resting or near-resting state. Exclude: stretching exercises **Comparison**: Include: no cool-down exercises **Outcome**: Include: health-outcomes related to muscle cramps/soreness/pain **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies.

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Law, 2007, Australia	Experimental: randomized controlled trial	52 healthy adults (23 men and 29 women aged 17 to 40 years) that performed exercise to induce delayed-onset muscle soreness (walking backwards downhill on an inclined treadmill for 30 minutes	Intervention 1: warm-up and cool-down exercise (walking forwards uphill on an inclined treadmill for (2x) 10 minutes) Intervention 2: cool-down only Control: no warm-up/cool-down	The sample size of 52 participants was determined prior to the conduct of the study. This sample size was sufficient to provide a better than 90% probability of detecting an effect of 20 mm on visual analogue scale soreness at 48 hours for either warm-up or cool-down, assuming within-cell standard deviations of 20 mm.
Olsen, 2012, Norway	Experimental: randomized controlled trial	36 volunteers (21 women, 15 men) performed leg resistance exercises (front lunges (10x5 repetitions/sets) with external loading of 40-50% of body mass. They were randomly assigned to cool-down group (intervention) or no cool-down (control)	Intervention: Cool-down (20 minutes cycling after resistance training) Control: No cool-down	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Warm-up and cool-down vs no warm-up/cool-down				
Muscle soreness (VAS 0-100) at 24 hours post-exercise	Warm-up and cool-down vs no warm-up/cool-down	Not statistically significant: 24±19 vs 33±18 MD: -9.00 95%CI [-23.23;5.23] (p=0.22) ¥	1, 13 vs 13 (power-analysis)	Law, 2007
Muscle soreness (VAS 0-100) at 48 hours post-exercise		Not statistically significant: 27±16 vs 40±19 MD: -13.00 95%CI [-26.50;0.50] (p=0.06) ¥		
Muscle soreness (VAS 0-100) at 72 hours post-exercise		Not statistically significant: 17±12 vs 25±17 MD: -8.00 95%CI [-19.31;3.31] (p=0.17)		
Cool-down vs no warm-up/cool-down				
Muscle soreness (VAS 0-100) at 24 hours post-exercise	Cool-down vs no warm-up/cool-down	Not statistically significant: 39±22 vs 33±18 MD: 6.00 95%CI [-9.45;21.45] (p=0.45) ¥	1, 13 vs 13 (power-analysis)	Law, 2007
Muscle soreness (VAS 0-100) at 48 hours post-exercise		Not statistically significant: 45±18 vs 40±19 MD: 5.00 95%CI [-9.23;19.23] (p=0.49)		
		Not statistically significant: 7 (0-42) (median and range) vs 14 (0-28) £ † (p>0.05)	1, 12 vs 12 §	Olsen, 2012
Muscle soreness (VAS 0-100) at 72 hours post-exercise		Not statistically significant: 27±24 vs 25±17 MD: 2.00 95%CI [-13.99;17.99] (p=0.81)		
		Not statistically significant: 8 (0-39) (median and range) vs 14 (0-54) £ † (p>0.05)	1, 12 vs 12 §	Olsen, 2012

Mean ± SD (unless otherwise indicated)
§ Imprecision (limited sample size)
¥ Imprecision (large variability of results)
£ No raw data/SD's/effect size/CI available
† Imprecision (lack of data)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Law, 2007	No	No	No	No	
Olsen, 2012	Unclear	No	No	No	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Limited sample size and large variability in results
Inconsistency	0	
Indirectness	-1	Soreness as indirect outcome for muscle cramps
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is limited evidence neither in favour of cooling-down exercises (with or without warming-up exercises) or no cooling-down exercises A statistically significant reduced muscle soreness, using cooling-down exercises compared to no cooling-down exercises, could not be demonstrated (Law 2007, Olsen 2012). Evidence is of low quality and results are imprecise due to limited sample size and large variability in results.
Reference(s)	**Articles** Law RY, Herbert RD. *Warm-up reduces delayed onset muscle soreness but cool-down does not: a randomised controlled trial*. Aust J Physiother. 2007, 53(2):91-5. Olsen O, Sjøhaug M, van Beekvelt M, Mork PJ. *The effect of warm-up and cool-down exercise on delayed onset muscle soreness in the quadriceps muscle: a randomized controlled trial*. J Hum Kinet. 2012, 35:59-68.

Muscle cramps – Drinking (Prevention)

Question (PICO)	In people (P), is drinking fluids before exercise (I) effective as prevention of exercise-associated muscle cramps (O) compared to drinking no fluids before exercise (C)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "muscle cramp"] OR [mh "musculoskeletal pain"] OR [mh "athletic injuries"] OR cramp:ti,ab,kw OR cramps:ti,ab,kw OR "delayed onset muscle soreness":ti,ab,kw OR "delayed onset muscular soreness":ti,ab,kw 2. [mh drinking] OR drink*:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for systematic reviews, experimental and observational studies using the following search strategy: 1. "muscle cramp"[Mesh] OR "musculoskeletal pain"[mesh] OR "athletic injuries"[Mesh] OR "cramp"[TIAB] OR "cramps"[TIAB] OR "delayed onset muscle soreness"[TIAB] OR "delayed onset muscular soreness"[TIAB] 2. drinking[Mesh] OR drink*[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) for systematic reviews, experimental and observational studies using the following search strategy: 1. 'muscle cramp'/exp OR 'musculoskeletal pain'/exp OR 'sport injury'/exp OR cramp:ab,ti OR cramps:ab,ti OR 'delayed onset muscle soreness':ab,ti OR 'delayed onset muscular soreness':ab,ti 2. drinking/exp OR drink*:ab,ti 3. 1-2 AND
Search date	09 September 2015
In/Exclusion criteria	**Population**: Include: people of all ages **Intervention**: Include: drinking (extra) fluids before the start of any exercise **Comparison:** Include: drinking no fluids before the start of any exercise **Outcome**: Include: (in-)direct outcomes related to exercise-related muscle cramps **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available.

	An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies. **Language:** Include: English. **Publication year:** Include: All years.

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Compartment syndrome – Posture (First Aid)

Question (PICO)	In humans with compartment syndrome (P), is a certain posture of the limb (I), compared to another posture of the limb (C) effective to reduce the pain (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "anterior compartment syndrome"] OR "compartment syndrome":ti,ab,kw OR "compartment syndromes":ti,ab,kw 2. [mh posture] OR posture*:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for systematic reviews, experimental and observational studies using the following search strategy: 1. "anterior compartment syndrome"[Mesh] OR "compartment syndrome"[TIAB] OR "compartment syndromes"[TIAB] 2. "posture"[Mesh] OR posture*[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) for systematic reviews, experimental and observational studies using the following search strategy: 1. 'compartment syndrome'/exp OR 'compartment syndrome':ab,ti OR 'compartment syndromes':ab,ti 2. 'body posture'/exp OR posture*:ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in MEDLINE (via PubMed interface).
Search date	11 September 2015
In/Exclusion criteria	**Population**: Include: people with diagnosis/symptoms of compartment syndrome or healthy volunteers **Intervention**: Include: any body position that can be provided by lay people **Comparison**: Include: studies that compare different body positions **Outcome**: Include: direct pain-related outcomes (e.g. muscle soreness) or indirect outcomes such as intracompartmental pressures.

	Design: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies.

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Meyer, 2002, USA	Experimental: non-randomized controlled trial (within-subjects design)	8 healthy volunteers (7 men, 1 woman, mean age 27 years) were positioned on a fracture table in 3 different postures	Intervention 1: the left leg in the hemilithotomy position with the calf supported (20-40 minutes) Intervention 2: the left leg in the hemilithotomy position with the heel supported but the calf free (40-60 minutes) Control: the left leg in the supine position (0-20 minutes))	The right leg was kept supine on the table
Pfeffer, 2001, USA	Experimental: randomized controlled trial (within-subjects design)	25 healthy volunteers (12 women and 13 men) between the ages of 20 and 36 years were studies in the awake state	Intervention 1: lithotomy position with the calf supported (right leg) Intervention 2: lithotomy position with the knee supported (right leg) Intervention 3: lithotomy position with the knee + calf supported (right leg) Intervention 4: lithotomy position with the heel supported (right leg) Control: Supine position	After instrumentation, the subject was allowed to rest supine for 30 min before measurements were performed. Subsequently, intracompartment pressure was measured for 30 min in each of the positions.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Average intramuscular pressure (mm Hg) anterior compartment	hemilithotomy position with the calf supported vs supine position	Statistically significant: 19.0±5.6 vs 11.0±5.6, MD: 8.0 £ (p<0.05) λ *In favour of supine position*	1, 8 vs 8 § (within subjects design)	Meyer, 2002
Average intramuscular		Statistically significant:		

pressure (mm Hg) lateral compartment		26.0±5.6 vs 13.0±2.8, MD: 13.0 £ (p<0.05) λ *In favour of supine position*		
Average intramuscular pressure (mm Hg) superficial posterior compartment		Not statistically significant: 15.0±8.5 vs 12.0±5.6, MD: 3.0 £† (p>0.05) λ		
Average intramuscular pressure (mm Hg) deep posterior compartment		Not statistically significant: 19.0±8.5 vs 13.0±5.6, MD: 6.0 £† (p>0.05) λ		
Average intracompartment pressure (mm Hg)		Statistically significant: 17.5±2.6 vs 10.5±6.9, MD: 7.0 £ (p<0.05) *In favour of supine position*	1, 25 vs 25 § (within subjects design)	Pfeffer, 2001
	hemilithotomy position with the knee supported vs supine position	Not statistically significant: 13.9±4.1 vs 11.0±1.2, MD: 2.9 £† (p>0.05)		
	hemilithotomy position with the knee+calf supported vs supine position	Statistically significant: 16.5±3.4 vs 10.7±5.8, MD: 5.8 £ (p<0.05) *In favour of supine position*		
Average intramuscular pressure (mm Hg) anterior compartment	hemilithotomy position with the heel supported vs supine position	Statistically significant: 3.0±2.8 vs 11.0±5.6, MD: -8.0 £ (p<0.05) λ *In favour of hemilithotomy position with the heel supported*	1, 8 vs 8 § (within subjects design)	Meyer, 2002
Average intramuscular pressure (mm Hg) lateral compartment		Statistically significant: 3.5±2.8 vs 13.0±2.8, MD: -9.5 £ (p<0.05) *In favour of hemilithotomy position with the heel supported*		
Average intramuscular pressure (mm Hg) superficial posterior compartment		Statistically significant: 2.0±2.8 vs 12.0±5.6, MD: -10.0 £ (p<0.05) λ *In favour of hemilithotomy position with the heel supported*		
Average intramuscular pressure (mm Hg) deep posterior compartment		Statistically significant: 2.0±5.6 vs 13.0±5.6, MD: -11.0 £ (p<0.05) λ *In favour of hemilithotomy position with the heel supported*		
Average intracompartment pressure (mm Hg)		Statistically significant: 8.7±5.6 vs 13.3±5.1, MD: -4.6 £ (p<0.05) *In favour of hemilithotomy position with the heel supported*	1, 25 vs 25 § (within subjects design)	Pfeffer, 2001

§ Imprecision (limited sample size)
£ No CI available
† Imprecision (lack of data)
λ Data extracted from graph

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Meyer, 2002	Unclear	Unclear	No	No	Within-subjects design, no randomisation
Pfeffer, 2001	Unclear	Unclear	No	No	Within-subjects design

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See 'Quality of evidence' table
Imprecision	-1	Limited sample size
Inconsistency	0	
Indirectness	-1	Indirect population (healthy volunteers) and indirect outcome (intracompartiment pressure)
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Conclusion	**Lithothomy position with the calf (and knee) supported** There is limited evidence in favour of the supine position. It was shown that the lithothomy position with the calf (and knee) supported resulted in a statistically significant increased intracompartment pressure, compared to the supine position (Meyer 2002, Pfeffer 2001). A statistically significant increased intracompartment pressure (superficial posterior compartment), using lithothomy position with the calf/knee supported compared to the supine position, could not be demonstrated. Evidence is of very low quality and results cannot be considered precise due to the limited sample size. **Lithothomy position with the heel supported** There is limited evidence in favour of the lithothomy position with the heel supported. It was shown that the lithothomy position with the heel supported resulted in a statistically significant decreased intracompartment pressure, compared to the supine position (Meyer 2002, Pfeffer 2001). Evidence is of very low quality and results cannot be considered precise due to the limited sample size.
Reference(s)	**Individual studies** Meyer RS, White KK, Smith JM, Groppo ER, Mubarak SJ, Hargens AR. *Intramuscular and blood pressures in legs positioned in the hemilithotomy position : clarification of risk factors for well-leg acute compartment syndrome*. J Bone Joint Surg Am. 2002;84-A(10):1829-1835. Pfeffer SD, Halliwill JR, Warner MA. *Effects of lithotomy position and external compression on lower leg muscle compartment pressure*. Anesthesiology. 2001;95(3):632-636.

Compartment syndrome – Rest (First Aid)

Question (PICO)	In humans (P), is rest (I) effective as treatment of compartment syndrome (O) compared to no rest (C)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "anterior compartment syndrome"] OR "compartment syndrome":ti,ab,kw OR "compartment syndromes":ti,ab,kw 2. [mh "Restraint, Physical"] OR [mh immobilization] OR [mh Rest] OR physical restraint:ti,ab,kw OR immobilization:ti,ab,kw OR immobilisation:ti,ab,kw OR rest:ti,ab,kw 3. 1-2 AND

	MEDLINE (via PubMed interface) for systematic reviews, experimental and observational studies using the following search strategy: 1. "anterior compartment syndrome"[Mesh] OR "compartment syndrome"[TIAB] OR "compartment syndromes"[TIAB] 2. "Restraint, Physical"[Mesh] OR immobilization[Mesh:NoExp] OR Rest[Mesh] OR physical restraint[TIAB] OR immobilisation[TIAB] OR immobilization [TIAB] OR rest[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) for systematic reviews, experimental and observational studies using the following search strategy: 1. 'compartment syndrome'/exp OR 'compartment syndrome':ab,ti OR 'compartment syndromes':ab,ti 2. 'rest'/exp OR 'physical restraint':ab,ti OR immobilization:ab,ti OR immobilisation:ab,ti OR rest:ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	11 September 2015
In/Exclusion criteria	**Population**: Include: people with diagnosis/symptoms of compartment syndrome **Intervention**: Include: exercise cessation, rest, immobilization **Comparison**: Include: exercise **Outcome**: Include: direct pain-related outcomes (e.g. muscle soreness). Exclude: indirect outcomes such as intracompartmental pressure. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised (un)controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies.

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Birtles, 2002, United Kingdom	Experimental: uncontrolled before-after study	20 patients (27.6±4.7 years, 16 males) with chronic exertional compartment syndrome (CECS)	All patients performed a 20-minute isometric exercise protocol consisting of intermittent maximal voluntary contractions.	
Kostopoulos, 2004, Greece	Experimental: uncontrolled before-after study	24 male patients (21.08±2.63 years) with chronic compartment syndrome (CACS)-related symptoms	All patients performed an intense 10-minute basketball-simulated exercise.	Outcomes were measured at rest (before) and 1 minute, 24 hours, 48 hours, 72 hours and 96 hours post-exercise

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Muscle soreness (VAS 0-10)	At rest vs 1-minute post-exercise	Statistically significant: 1.0±0.0 vs 8.9±1.5, MD: -7.9 £ (p<0.05) *In favour of rest*	1, 24 vs 24 § (before-after study)	Kostopoulos, 2004
Pain (VAS 0-10)		Statistically significant: £ † (p<0.001) *In favour of rest*	1, 20 vs 20 § (before-after study)	Birtles, 2002
	At rest vs 4-minutes post-exercise	Statistically significant: £ † (p<0.05) *In favour of rest*		
Muscle soreness (VAS 0-10)	At rest vs 24 hours post-exercise	Statistically significant: 1.0±0.0 vs 6.5±0.7, MD: -5.5 95% CI not estimable* (p<0.05) *In favour of rest*	1, 24 vs 24 § (before-after study)	Kostopoulos, 2004
	At rest vs 48 hours post-exercise	Statistically significant: 1.0±0.0 vs 8.2±1.1, MD: -7.2 £(p<0.05) *In favour of rest*		
	At rest vs 72 hours post-exercise	Statistically significant: 1.0±0.0 vs 6.5±1.0, MD: -5.5 £(p<0.05) *In favour of rest*		
	At rest vs 96 hours post-exercise	Statistically significant: 1.0±0.0 vs 3.8±0.6, MD: -2.8 £(p<0.05) *In favour of rest*		

Mean ± SD
§ Imprecision (limited sample size)
£ No raw data/SD's/effect size/CI available

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Birtles, 2002	Unclear	Unclear	No	No	Before-after study
Kostopoulos, 2004	Unclear	Yes	No	No	Before-after study

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See 'Quality of evidence' table
Imprecision	-1	Limited sample size
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is limited evidence in favour of rest. It was shown that rest resulted in a statistically significant reduced muscle soreness/pain, compared to performing exercise (Birtles 2002, Kostopoulos 2004). Evidence is of low quality and results cannot be considered precise due to the limited sample size.

Reference(s)	**Individual studies** Birtles DB, Minden D, Wickes SJ, M Puxley KP, A Llewellyn MG, Casey A, Rayson MP, Jones DA, Newham DJ. *Chronic exertional compartment syndrome: muscle changes with isometric exercise*. Med Sci Sports Exerc. 2002;34(12):1900-1906. Kostopoulos N, Fatouros IG, Siatitsas I, Baltopoulos P, Kambas A, Jamurtas AZ, Fotinakis P. *Intense basketball-simulated exercise induces muscle damage in men with elevated anterior compartment pressure*. J Strength Cond Res. 2004;18(3):451-458.

Dislocation – Rest (First Aid)

Question (PICO)	In humans with a dislocation (P), is rest (I) compared to no rest (C) effective to improve health outcomes (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh Dislocations] OR dislocat*:ti,ab,kw 2. [mh "Restraint, Physical"] OR [mh immobilization] OR [mh Rest] OR physical restraint:ti,ab,kw OR immobilization:ti,ab,kw OR immobilization:ti,ab,kw OR rest:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Dislocations[Mesh] OR dislocat*[TIAB] 2. "Restraint, Physical"[Mesh] OR immobilization[Mesh:NoExp] OR Rest[Mesh] OR physical restraint[TIAB] OR immobilization[TIAB] OR immobilization [TIAB] OR rest[TIAB] 3. "Guideline "[Publication Type] OR "Practice Guidelines as Topic"[Mesh] OR "Practice Guideline "[Publication Type] OR practice guideline*[TIAB] OR Meta-Analysis as Topic[Mesh] OR meta analy*[TIAB] OR metaanaly*[TIAB] OR Meta-Analysis[Publication Type] OR systematic review*[TIAB] OR systematic overview*[TIAB] OR Review Literature as Topic[Mesh] OR cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB] OR reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB] OR selection criteria[TIAB] OR data extraction[TIAB] AND Review[PT] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. dislocation/exp OR dislocat*:ab,ti 2. 'rest'/exp OR 'physical restraint':ab,ti OR immobilization:ab,ti OR immobilisation:ab,ti OR rest:ab,ti 3. 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti 4. 1-3 AND Guidelines, systematic reviews, retrieved with the above searches, and used as source for individual studies: Jones, 2007 Kerkhoffs, 2002 Kerkhoffs, 2012

	van den Bekerom, 2012
Search date	24 September 2015
In/Exclusion criteria	**Population**: Include: people with dislocation(s). Exclude: surgical settings. **Intervention**: Include: rest/immobilization. **Comparison**: Include: no rest/exercise/mobilization **Outcome**: Include: functional recovery, pain, swelling, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Taylor, 2012, New Zealand	(Cochrane) systematic review	2 small randomized controlled trials of conservative and surgical treatment of dislocations of the elbow in adults, involving a total of 80 participants with simple elbow dislocations. Excluded were trials involving dislocations with associated fractures, except for avulsion fractures.	Intervention: non-operative: closed reduction, post reduction cast immobilization, post reduction functional bracing, early mobilization, late mobilization Control: operative: open reduction, medial soft tissue repair, lateral soft tissue repair, external fixation	Review content assessed as up-to-date: 1 July 2011
Rafai, 1999, Maroc	Experimental: randomized controlled trial	50 participants with posterior dislocation of the elbow (43 male, mean age 25 years, range 16 to 67 years)	Intervention: immobilization: plaster cast immobilization at 90 degrees for 3 weeks, followed by rehabilitation. Control: early mobilization: mobilization started after 3 days. Self-rehabilitation at 3 times a day for 10 minutes increasing range of mobilization over time. For the first 3 weeks, the arm was kept in a sling when not exercising.	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Incomplete recovery of extension/flexion/ pronosupination at 12 months	Cast immobilization vs early mobilization	Not statistically significant: 5/26 vs 1/24 § RR: 4.62, 95%CI [0.58;36.73]* ¥ (p=0.15)	1, 26 vs 24	Rafai, 1999
Residual pain		Not statistically significant: 1/26 vs 1/24 § RR: 0.92, 95%CI [0.06;13.95]* ¥ (p=0.95)		
Instability/recurrence		Not statistically significant: 0/26 vs 0/24 § RR: not estimable* † (p=1.00)		

*Calculations done by the reviewer(s) using Review Manager software
¥ Imprecision (large variability of results)
§ Imprecision (low number of events)
† Imprecision (lack of data)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Rafai, 1999	Unclear	Yes	Unclear	Unclear	Unclear

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Low number of events, large variability of the results or lack of data
Inconsistency	0	
Indirectness	-1	Immobilization by plaster cast
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Conclusion	There is limited evidence neither in favour of rest (immobilization by plaster cast) nor early mobilization. A statistically significant increased rate of elbow flexion/extension recovery and a decreased residual pain, instability or recurrence, using plaster cast immobilization (rest) compared to early mobilization, could not be demonstrated (Rafai 1999). Evidence is of very low quality and results of this study are imprecise due to limited sample size and large variability of results.
Reference(s)	**Articles** Rafai M, Largab A, Cohen D, Trafeh M. *Pure posterior luxation of the elbow in adults: immobilization or early mobilization. A randomized prospective study of 50 cases.* Chir Main. 1999;18(4):272-278. **Systematic reviews** Taylor F, Sims M, Theis JC, Herbison GP. *Interventions for treating acute elbow dislocations in adults*. Cochrane Database Syst Rev. 2012 Apr 18;4:CD007908.

Broken and dislocated limbs – Sling (First Aid)

Question (PICO)	Among persons with a broken or dislocated limb (P), does application of a sling (I) compared to no application of a sling (C) change functional recovery, pain, complications, time to resolution of symptoms (O)?
Search Strategy	Databases: **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Fractures, Bone"] OR [mh "Dislocations"] OR [mh "fracture healing"] OR ("fracture"):ti,ab,kw OR (("broken"):ti,ab,kw AND ("bone"):ti,ab,kw) OR ("dislocation"):ti,ab,kw OR ("subluxation"):ti,ab,kw 2. [mh immobilization] or 'immobilization':ti,ab,kw or 'immobilisation':ti,ab,kw or (restrict*):ti,ab,kw or (stabiliz*):ti,ab,kw or (stabilis*):ti,ab,kw or (restraint*):ti,ab,kw 3. (splint*):ti,ab,kw or (sling*):ti,ab,kw or (device*):ti,ab,kw or (bandage*):ti,ab,kw 4. 1-3 and **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Fractures, Bone"[Mesh] OR "Dislocations"[Mesh] OR "fracture healing"[Mesh] OR "fracture"[TIAB] OR ("broken"[TIAB] AND "bone"[TIAB]) OR "dislocation"[TIAB] OR "subluxation"[TIAB] 2. "Immobilization"[Mesh] OR immobiliz* [TIAB] OR immobilis* [TIAB] OR Emergency Medical Services/methods [Mesh] OR restrict* [TIAB] OR restain*[TIAB] OR stabiliz*[TIAB] OR stabilis*[TIAB] 3. sling*[TIAB] OR splint*[TIAB] OR device*[TIAB] OR bandage*[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'dislocation'/exp OR 'fracture'/exp OR 'fracture healing'/exp OR fracture OR (bone AND broken) OR 'dislocation':ab:ti OR 'subluxation':ab:ti 2. 'fracture immobilization'/exp OR immobiliz*:ab:ti OR immobilis*:ab:ti OR restrict*:ab:ti OR restrain*:ab:ti OR stabiliz*:ab:ti OR stabilis*:ab:ti 3. sling*:ab:ti OR splint*:ab:ti OR device*:ab:ti OR bandage*ab:ti 4. 1-3 AND
Search date	04 March 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. We did not include long-term therapies, or plaster therapies. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available.

	An observational study: <u>inclusion</u> in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. <u>Exclude</u>: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies. **Language**: <u>Include</u>: English **Publication year**: <u>Include</u>: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

<u>Broken and dislocated limbs – Splint vs sling (First Aid)</u>

Question (PICO)	Among persons with a broken or dislocated limb (P), does immobilisation (I) compared to application of a sling (C) change functional recovery, pain, complications, time to resolution of symptoms (O)?
Search Strategy	<u>Databases</u> **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Fractures, Bone"] OR [mh "Dislocations"] OR [mh "fracture healing"] OR ("fracture"):ti,ab,kw OR (("broken"):ti,ab,kw AND ("bone"):ti,ab,kw) OR ("dislocation"):ti,ab,kw OR ("subluxation"):ti,ab,kw 2. [mh immobilization] or 'immobilization':ti,ab,kw or 'immobilisation':ti,ab,kw or (restrict*):ti,ab,kw or (stabiliz*):ti,ab,kw or (stabilis*):ti,ab,kw or (restraint*):ti,ab,kw 3. (splint*):ti,ab,kw or (sling*):ti,ab,kw or (device*):ti,ab,kw or (bandage*):ti,ab,kw 4. 1-3 AND **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Fractures, Bone"[Mesh] OR "Dislocations"[Mesh] OR "fracture healing"[Mesh] OR "fracture"[TIAB] OR ("broken"[TIAB] AND "bone"[TIAB]) OR "dislocation"[TIAB] OR "subluxation"[TIAB] 2. "Immobilization"[Mesh] OR immobiliz* [TIAB] OR immobilis* [TIAB] OR Emergency Medical Services/methods [Mesh] OR restrict* [TIAB] OR restain*[TIAB] OR stabiliz*[TIAB] OR stabilis*[TIAB] 3. sling*[TIAB] OR splint*[TIAB] OR device*[TIAB] OR bandage*[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'dislocation'/exp OR 'fracture'/exp OR 'fracture healing'/exp OR fracture OR bone AND broken) OR 'dislocation':ab:ti OR 'subluxation':ab:ti 2. 'fracture immobilization'/exp OR immobiliz*:ab:ti OR immobilis*:ab:ti OR restrict*:ab:ti OR restrain*:ab:ti OR stabiliz*:ab:ti OR stabilis*:ab:ti 3. sling*:ab:ti OR splint*:ab:ti OR device*:ab:ti OR bandage*ab:ti 4. 1-3 AND
Search date	04 March 2015
In/Exclusion criteria	**Population**: <u>Include</u>: sick or injured people or healthy volunteers of all ages.

	Intervention: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. We did not include long-term therapies, or plaster therapies. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies. **Language**: Include: English **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Broken and dislocated limbs

Question (PICO)	Among persons with a broken or dislocated limb (P), does immobilization with a splint (I) compared to no immobilisation (C) change functional recovery, pain, complications, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Fractures, Bone"] OR [mh "Dislocations"] OR [mh "fracture healing"] OR ("fracture"):ti,ab,kw OR (("broken"):ti,ab,kw AND ("bone"):ti,ab,kw) OR ("dislocation"):ti,ab,kw OR ("subluxation"):ti,ab,kw 2. [mh immobilization] or 'immobilization':ti,ab,kw or 'immobilisation':ti,ab,kw or (restrict*):ti,ab,kw or (stabiliz*):ti,ab,kw or (stabilis*):ti,ab,kw or (restraint*):ti,ab,kw 3. (splint*):ti,ab,kw or (sling*):ti,ab,kw or (device*):ti,ab,kw or (bandage*):ti,ab,kw

	4. 1-3 and **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Fractures, Bone"[Mesh] OR "Dislocations"[Mesh] OR "fracture healing"[Mesh] OR "fracture"[TIAB] OR ("broken"[TIAB] AND "bone"[TIAB]) OR "dislocation"[TIAB] OR "subluxation"[TIAB] 2. "Immobilization"[Mesh] OR immobiliz* [TIAB] OR immobilis* [TIAB] OR Emergency Medical Services/methods [Mesh] OR restrict* [TIAB] OR restain*[TIAB] OR stabiliz*[TIAB] OR stabilis*[TIAB] 3. sling*[TIAB] OR splint*[TIAB] OR device*[TIAB] OR bandage*[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'dislocation'/exp OR 'fracture'/exp OR 'fracture healing'/exp OR fracture OR (bone AND broken) OR 'dislocation':ab:ti OR 'subluxation':ab:ti 2. 'fracture immobilization'/exp OR immobiliz*:ab:ti OR immobilis*:ab:ti OR restrict*:ab:ti OR restrain*:ab:ti OR stabiliz*:ab:ti OR stabilis*:ab:ti 3. sling*:ab:ti OR splint*:ab:ti OR device*:ab:ti OR bandage*ab:ti 4. 1-3 AND
Search date	04 March 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. We did not include long-term therapies, or plaster therapies. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies. **Language**: Include: English **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Fractures – Interventions to prevent factures (Prevention)

Question (PICO)	In elderly (P), which interventions (I) are effective to prevent fractures (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh fractures, bones] OR fracture:ti,ab,kw OR fractures:ti,ab,kw OR "broken bone":ti,ab,kw OR "broken bones":ti,ab,kw 2. [mh aged] OR [mh frail elderly] OR elderly:ti,ab,kw OR "older adults":ti,ab,kw 3. [mh risk factors] OR "risk factor":ti,ab,kw OR "risk factors":ti,ab,kw 4. 1-3 AND **MEDLINE** (via PubMed interface) for guidelines and systematic reviews using the following search strategy: 1. "Fractures, Bone"[Mesh] OR fracture[TIAB] OR fractures[TIAB] OR "broken bone"[TIAB] OR "broken bones"[TIAB] 2. Aged[Mesh] OR "frail elderly"[Mesh] OR elderly[TIAB] OR "older adults"[TIAB] 3. "Risk factors"[Mesh] OR "risk factor"[TIAB] OR "risk factors"[TIAB] 4. "Guideline "[Publication Type] OR "Practice Guidelines as Topic"[Mesh] OR "Practice Guideline "[Publication Type] OR practice guideline*[TIAB] OR Meta-Analysis as Topic[Mesh] OR meta analy*[TIAB] OR metaanaly*[TIAB] OR Meta-Analysis[Publication Type] OR systematic review*[TIAB] OR systematic overview*[TIAB] OR Review Literature as Topic[Mesh] OR cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB] OR reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB] OR selection criteria[TIAB] OR data extraction[TIAB] AND Review[PT] 5. 1-4 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Fracture/exp OR fracture:ab,ti OR factures:ab,ti OR 'broken bone':ab,ti OR 'broken bones':ab,ti 2. Aged/exp OR elderly:ab,ti OR 'older adults':ab,ti 3. 'Risk factor'/exp OR 'risk factor':ab,ti OR 'risk factors':ab,ti 4. 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti 5. 1-4 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in MEDLINE (via PubMed interface).
Search date	25 September 2015
In/Exclusion criteria	**Population:** Include: older adults (elderly) **Intervention**: Include: interventions aimed to reduce the risk of falls/fractures that can be performed by lay people (i.e. basic first responders, lay caregivers and/or community health workers). Exclude: medication use (e.g. Vitamin D), surgery, psychological/educational interventions, vision improvement, combinations of different type of interventions (eg exercise + footwear modification), multifactorial intervention, institutional settings (e.g. hospitals) **Comparison:** Include: no intervention or an intervention not expect to reduce falls and the corresponding risk fractures

	Outcome: Include: risk of fractures **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies.

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Gillespie, 2012, United Kingdom	Systematic review (Cochrane)	159 randomized trials with 79193 participants including interventions to reduce falls in community-dwelling older people compared to no intervention or an intervention not expected to reduce falls (control)	Intervention: interventions to reduce falls Control: no intervention or an intervention not expected to reduce falls	Last assessed as up-to-date: 1 March 2012
Santesso, 2014, United Kingdom	Systematic review (Cochrane)	19 (cluster) randomized controlled trials, including 17000 people (age ranged from 78 to 86 years), about the effectiveness of hip protectors in elderly people	Intervention: provision of hip protectors Control: no provision of hip protectors	Last assessed as up-to-date: 18 June 2013

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Exercise				
Number of people sustaining a fracture	Exercise vs control	Statistically significant: RR: 0.34, 95%CI [0.18;0.63] (p<0.00071) £ *In favour of exercise*	6, 401 vs 409	Gillespie, 2012
Environmental/assistive technology interventions				
Rate of falls	Home safety (adaptations to homes and the provision of aids for personal care and protection and personal mobility (e.g. walking aids) vs control	Statistically significant: RR: 0.81, 95%CI [0.68;0.97] (p=0.022) £ *In favour of home safety*	6, 1806 vs 2402	Gillespie, 2012
	Footwear modification (anti-slip shoe device for icy conditions) vs control	Statistically significant: RR: 0.42, 95%CI [0.22;0.78] (p=0.0066) £ *In favour of footwear modification*	1, 55 vs 54 (power-analysis)	
Hip protectors				
Risk for any hip fracture	Hip protectors vs no hip protectors	Not statistically significant: RR: 1.10, 95%CI [0.80;1.52] (p=0.55) £¥	4, 2013 vs 3235	Santesso, 2014

Risk for pelvic fracture		Not statistically significant: RR: 1.04, 95%CI [0.52;2.09] (p=0.91) £¥	3, 1872 vs 3263	
Risk for other fractures (excluding pelvis)		Not statistically significant: RR: 0.83, 95%CI [0.65;1.04] (p=0.11) £¥		
Risk for pelvic and other fractures		Not statistically significant: RR: 0.86, 95%CI [0.69;1.06] (p=0.17) £¥	5, 2195 vs 3419	

£ No raw data available
¥ Imprecision (large variability of results)

Level of evidence
Exercise

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See SR Gillespie 2012
Imprecision	0	
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Moderate [B]**	

Environmental/assistive technology interventions

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See SR Gillespie 2012
Imprecision	0	
Inconsistency	0	
Indirectness	-1	Rate of falls as indirect outcome for fracture risk
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Hip protectors

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See SR Santesso 2014
Imprecision	-1	Large variability of the results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	**Exercise** There is evidence in favour of exercise. It was shown that exercise resulted in a statistically significant decreased fracture risk, compared to no/sham intervention (Gillespie 2012). Evidence is of moderate quality. **Environmental/assistive technology interventions** There is limited evidence in favour of environmental/assistive technology interventions. It was shown that home safety interventions and footwear modification resulted in a statistically significant decreased rate of falling, compared to no/sham intervention (Gillespie 2012). Evidence is of low quality. **Hip protectors**

	There is limited evidence neither in favour of the intervention nor the control. A statistically significant decreased fracture risk, using hip protectors compared to no hip protectors, could not be demonstrated (Santesso 2014). Evidence is of low quality and results are imprecise due to large variability of results.
Reference(s)	**Systematic reviews** Gillespie LD, Robertson MC, Gillespie WJ, Sherrington C, Gates S, Clemson LM, Lamb SE. *Interventions for preventing falls in older people living in the community*. Cochrane Database Syst Rev. 2012, 12;9:CD007146. Santesso N, Carrasco-Labra A, Brignardello-Petersen R. *Hip protectors for preventing hip fractures in older people*. Cochrane Database Syst Rev. 2014, 31;3:CD001255.

STINGS AND BITES

Bee or wasp stings – Pinching or scraping (First aid)

Question (PICO)	Among persons with a bee/wasp sting (P), does pinching (I) compared to scraping to remove the sting (C) change functional recovery, pain, complications, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the search terms: [mh "Bees"] OR [mh "Wasps"] **MEDLINE** (via PubMed interface) using the following search strategy: 1. "bee"[Mesh] OR bee [TIAB] OR "wasp"[Mesh] OR wasp [TIAB] 2. "sting"[TIAB] AND ("remove"[TIAB] OR "removing"[TIAB] OR "removal"[TIAB] OR "extract"[TIAB] OR "extraction"[TIAB] OR "pinching"[TIAB] OR "scraping" [TIAB]) 3. 1 AND 2 **Embase** (via Embase.com interface) using the following search strategy: 1. 'bee sting'/exp OR 'wasp sting'/exp OR (('bee'/exp OR 'wasp'/exp OR bee*:ab,ti OR wasp*:ab,ti) AND sting*:ab,ti) 2. 'pinch':ab,ti OR 'pinching':ab,ti OR 'pinched':ab,ti OR 'scrape':ab,ti OR 'scraping':ab,ti OR 'scraped':ab,ti OR 'remove':ab,ti OR 'removal':ab,ti OR 'removing':ab,ti OR 'removed':ab,ti OR 'manage':ab,ti OR 'managing':ab,ti OR 'management':ab,ti OR 'managed':ab,ti 3. 1 AND 2 Selected articles were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	26 February 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies. **Language**: Include: English **Publication year**: Include: all years

Characteristics of included studies

Author, Year, Country	Study design	Population	Comparison	Remarks
Visscher, 1996, USA	Experimental: Randomized controlled trial	Two of the three authors were used as 'blinded volunteers', All stings were self-administered; each volunteer collected data on 10 stings of each treatment	Scraping versus pinching to remove bee stings.	There is no data related to the characteristics of the participants. There was no significant difference between volunteers or arms within volunteers.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Mean weal area at 10 min (mm^2)	Stings scraped vs. Stings pinched	Not statistically significant: 80±5.9 vs. 74±5.1 MD : 6.00 (p=0.42)	1, 20 vs 20 (stings) (within subjects design) §	Visscher, 1996

Mean ± SE

§ Imprecision (limited sample size)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Visscher, 1996	Yes – but shouldn't affect outcome	No	No	No	Small study. Not certain that you can consider the study participants 'volunteers' if they are also writing the paper.

Level of evidence

	Initial grading High (A)	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample size
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low (C)**	

Conclusion(s)	There is limited evidence neither in favour of scraping nor pinching: in one study, a statistically significant decrease of weal area using scraping (to remove a sting) compared to pinching could not be demonstrated (Visscher 1996). Evidence is of low quality and results of this study are imprecise due a limited sample size.
Reference(s)	Visscher PK, Vetter RS, Camazine S. *Removing bee stings*. Lancet 1996, 348(9023):301-302.

Bee or wasp stings – Quick removal (First aid)

Question (PICO)	Among persons with a bee/wasp sting (P), does quick removal of the sting (I) compared to no quick removal (C) change functional recovery, pain, complications, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the search terms: [mh "Bees"] OR [mh "Wasps"] **MEDLINE** (via PubMed interface) using the following search strategy: 1. "bee"[Mesh] OR bee [TIAB] OR "wasp"[Mesh] OR wasp [TIAB] 2. "sting"[TIAB] AND ("remove"[TIAB] OR "removing"[TIAB] OR "removal"[TIAB] OR "extract"[TIAB] OR "extraction"[TIAB] OR "pinching"[TIAB] OR "scraping" [TIAB]) 3. 1 AND 2 **Embase** (via Embase.com interface) using the following search strategy: 1. 'bee sting'/exp OR 'wasp sting'/exp OR (('bee'/exp OR 'wasp'/exp OR bee*:ab,ti OR wasp*:ab,ti) AND sting*:ab,ti) 2. 'pinch':ab,ti OR 'pinching':ab,ti OR 'pinched':ab,ti OR 'scrape':ab,ti OR 'scraping':ab,ti OR 'scraped':ab,ti OR 'remove':ab,ti OR 'removal':ab,ti OR 'removing':ab,ti OR 'removed':ab,ti OR 'manage':ab,ti OR 'managing':ab,ti OR 'management':ab,ti OR 'managed':ab,ti 3. 1 AND 2 Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	26 February 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies. **Language**: Include: English **Publication year**: Include: all years

Characteristics of included studies

Author, Year, Country	Study design	Population	Comparison	Remarks
Visscher, 1996, USA	Experimental: Randomized controlled trial	One of the three authors was used as 'blinded volunteer', All stings were self-administered; 10 stings for each treatment	Removal of sting after 0.5s, 1s, 2s, 4s, 8s	There is no data related to the characteristics of the participants. There was no significant difference between volunteers or arms within volunteers.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Mean weal area at 10 min (mm^2)	Removal of sting after 0.5s, 1s, 2s, 4s, 8s	Statistically significant: 0.5s: 62±5.8 1s: 62±5.0 2s: 65±7.9 4s: 69±8.3 8s: 82±9.2 (p=0.018) No effect size and CI available.	1, 20 stings vs 20 stings (within subjects design) §	Visscher, 1996

Mean ± SE

§ Imprecision (limited sample size)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Visscher, 1996	Yes – but shouldn't affect outcome	No	No	No	Small study. Not certain that you can consider the study participants 'volunteers' if they are also writing the paper.

Level of evidence

	Initial grading High (A)	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample size
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low (C)**	

Conclusion(s)	There is limited evidence in favour of a quick removal of the sting: in one study, a statistically significant increase of weal area with time of removal was shown (Visscher 1996). Evidence is of low quality and results of this study are imprecise due a limited sample size.
Reference(s)	Visscher PK, Vetter RS, Camazine S. *Removing bee stings*. Lancet 1996, 348(9023):301-302.

Insect sting – Ice (First aid)

Question (PICO)	Among persons with an insect sting (P), does cooling with ice (I) compared to not cooling with ice (C) change functional recovery, pain, complications, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "Bees"] OR [mh "Wasps"] OR [mh "Culicidae"] **MEDLINE** (via PubMed interface) using the following search strategy: 4. "bees"[Mesh] OR bee[TIAB] OR bees[TIAB] OR "wasps"[Mesh] OR wasp*[TIAB] OR "Culicidae"[Mesh] OR mosquito*[TIAB] 5. Ice[Mesh] OR ice[TIAB] OR cryotherapy[Mesh] OR cryotherapy[TIAB] 6. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 4. 'bee sting'/exp OR 'wasp sting'/exp OR 'mosquito bite'/exp OR (('bee'/exp OR 'wasp'/exp OR 'mosquito'/exp OR bee*:ab,ti OR wasp*:ab,ti OR mosquito*:ab,ti) AND sting*:ab,ti) 5. Ice/exp OR ice:ab,ti OR cryotherapy/exp OR cryotherapy:ab,ti 6. 1-2 AND
Search date	17 June 2015
In/Exclusion criteria	**Population**: Include: people or healthy volunteers with a bee/wasp/mosquito sting **Intervention**: Include: use of ice, cold pack, ice pack **Outcome**: Include: functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion(s)	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Bee or wasp stings – Vinegar (First aid)

Question (PICO)	Among persons with a bee/wasp sting (P), does application of vinegar (I) compared to no application of vinegar (C) change functional recovery, pain, complications, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the search terms: [mh "Bees"] OR [mh "Wasps"] **MEDLINE** (via PubMed interface) using the following search strategy: 1. "bees"[Mesh] OR bee[TIAB] OR bees[TIAB] OR "wasps"[Mesh] OR wasp*[TIAB] 2. "Bites and Stings"[Mesh] OR sting*[TIAB] 3. "Acetic Acid"[Mesh] OR vinegar [TIAB] OR acetic acid [TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'bee sting'/exp OR 'wasp sting'/exp OR (('bee'/exp OR 'wasp'/exp OR bee*:ab,ti OR wasp*:ab,ti) AND sting*:ab,ti) 2. 'vinegar'/exp OR vinegar:ti,ab OR 'acetic acid':ti,ab 3. 1-2 AND
Search date	12 June 2015
In/Exclusion criteria	**Population**: Include: people or healthy volunteers with a bee/wasp sting **Intervention**: Include: use of vinegar **Outcome**: Include: functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies. **Language**: Include: English **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion(s)	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Itch – Itch soothing solution (First Aid)

Question (PICO)	In humans with itch due to a bite or a sting (P), is the use of itch-soothing crème or lotion (I) compared to not using this (C) effective to reduce itching (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Bites and stings"] OR mosquito*:ti,ab,kw OR bee*:ti,ab,kw OR wasp*:ti,ab,kw OR tick*:ti,ab,kw OR caterpillar*:ti,ab,kw OR Thaumotopoea:ti,ab,kw OR "Oak processionary":ti,ab,kw OR "caterpillar dermatitis":ti,ab,kw OR Lepidoptera:ti,ab,kw OR scorpion*:ti,ab,kw OR spider*:ti,ab,kw OR "Scyphozoa":ti,ab,kw OR [mh "Cubozoa"] OR jellyfish:ti,ab,kw OR Scyphozoa:ti,ab,kw OR Cubozoa:ti,ab,kw OR [mh "Sea Urchins"] OR [mh "Fishes, Poisonous"] OR urchin:ti,ab,kw OR hedgehog:ti,ab,kw OR "sand dollar*":ti,ab,kw OR "trachinus vipera":ti,ab,kw 2. [mh ointments] OR [mh emollients] OR ointment*:ti,ab,kw OR salve*:ti,ab,kw OR spray*:ti,ab,kw OR lotion*:ti,ab,kw OR solution*:ti,ab,kw OR emollient*:ti,ab,kw 3. itch*:ti,ab,kw OR sooth*:ti,ab,kw 4. 1-3 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Bites and stings"[Mesh] OR mosquito*[TIAB] OR bee*[TIAB] OR wasp*[TIAB] OR tick*[TIAB] OR caterpillar*[TIAB] OR Thaumotopoea[TIAB] OR Oak processionary[TIAB] OR caterpillar dermatitis[TIAB] OR lepidoptera[TIAB] OR scorpion*[TIAB] OR spider*[TIAB] OR Scyphozoa[Mesh] OR Cubozoa[Mesh] OR jellyfish[TIAB] OR Scyphozoa[TIAB] OR Cubozoa[TIAB] OR "Sea Urchins"[Mesh] OR "Fishes, Poisonous"[Mesh] OR urchin[TIAB] OR hedgehog[TIAB] OR sand dollar*[TIAB] OR trachinus vipera[TIAB] 2. ointments[Mesh] OR emollients[Mesh] OR ointment*[TIAB] OR salve*[TIAB] OR spray*[TIAB] OR lotion*[TIAB] OR solution*[TIAB] OR emollient*[TIAB] 3. itch*[TIAB] OR sooth*[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'Bites and stings'/exp OR mosquito*:ab,ti OR bee*:ab,ti OR wasp*:ab,ti OR tick*:ab,ti OR caterpillar*:ab,ti OR Thaumotopoea:ab,ti OR 'Oak processionary':ab,ti OR 'caterpillar dermatitis':ab,ti OR Lepidoptera:ab,ti OR scorpion*:ab,ti OR spider*:ab,ti OR jellyfish/exp OR Cubozoa/exp OR jellyfish:ab,ti OR Scyphozoa:ab,ti OR Cubozoa:ab,ti OR 'Sea Urchin'/exp OR 'toxic fish'/exp OR urchin:ab,ti OR hedgehog:ab,ti OR (sand NEXT/1 dollar*):ab,ti OR 'trachinus vipera':ab,ti 2. ointment/de OR 'emollient agent'/exp OR ointment*:ab,ti OR salve*:ab,ti OR spray*:ab,ti OR lotion*:ab,ti OR solution*:ab,ti OR emollient*:ab,ti 3. itch*:ab,ti OR sooth*:ab,ti 4. 1-3 AND
Search date	6 November 2015
In/Exclusion criteria	**Population**: People with stings or bites from insects, scorpions, spiders, oak processary caterpillars, jellyfish or sea animals. **Intervention**: itch-soothing cream or lotions. **Comparison**: no intervention. **Outcome**: relief of itch. **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available.

	An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Bee or wasp stings – Suction devices (First aid)

Question (PICO)	Among persons with a bee/wasp sting (P), does the use of suction devices (I) compared to no use of suction devices (C) change functional recovery, pain, complications, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "Bees"] OR [mh "Wasps"] **MEDLINE** (via PubMed interface) using the following search strategy: 1. "bee"[Mesh] OR bee[TIAB] OR bees[TIAB] OR "wasp"[Mesh] OR wasp*[TIAB] 2. "Bites and Stings"[Mesh] OR sting*[TIAB] 3. suction[Mesh] OR extract*[TIAB] OR suction*[TIAB] OR suck*[TIAB] OR aspirat*[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) for experimental and observational studies using the following search strategy: 1. 'bee sting'/exp OR 'wasp sting'/exp OR (('bee'/exp OR 'wasp'/exp OR bee*:ab,ti OR wasp*:ab,ti) AND sting*:ab,ti) 2. suction/exp OR extract*:ab,ti OR suction*:ab,ti OR suck*:ab,ti OR aspirat*:ab,ti 3. 1-2 AND
Search date	11 June 2015
In/Exclusion criteria	**Population**: Include: people or healthy volunteers with a bee/wasp sting **Intervention**: Include: use of suction device **Outcome**: Include: functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched.

	An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion(s)	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Bee or wasp stings (First aid)

Question (PICO)	Among persons with a bee/wasp sting (P), does application of topical aspirin (I) compared to no application of topical aspirin (C) change functional recovery, pain, complications, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the search terms: [mh "Bees"] OR [mh "Wasps"] **MEDLINE** (via PubMed interface) for guidelines, systematic reviews or experimental studies using the following search strategy: 1. "bee"[Mesh] OR bee [TIAB] OR "wasp"[Mesh] OR wasp [TIAB] 2. "Aspirin"[Mesh] OR Aspirin [TIAB] OR "acetylsalicylic acid"[TIAB] 3. 1 AND 2 **Embase** (via Embase.com interface) for systematic reviews or experimental studies using the following search strategy: 1. 'bee sting'/exp OR 'wasp sting'/exp OR (('bee'/exp OR 'wasp'/exp OR bee*:ab,ti OR wasp*:ab,ti) AND sting*:ab,ti) 2. 'acetylsalicylic acid'/exp OR 'aspirin':ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	26 February 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered

	as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies. **Language**: Include: English **Publication year**: Include: all years

Characteristics of included studies

Author, Year, Country	Study design	Population	Comparison	Remarks
Balit, 2003 Australia	Experimental: Randomised controlled trial	60 Patients calling the New South Wales Poisons Information Centre reporting a bee or wasp sting; 40 were assigned to treatment group (3 excluded), 20 to control group (1 excluded)	Ice pack and topical aspirin applied to lesion compared with ice pack alone.	It was noted that 27 of the 37 patients included in treatment arm applied aspirin as instructed and 18 of the 19 patients in the control arm applied ice as instructed. The final calculations were based on ITT analysis. Initial follow up was within 24-48 hrs.

ITT: intention to treat

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
No swelling at 12 hr *(Primary outcome)*	Topical aspirin + ice pack vs Ice pack alone	Not statistically significant: ITT analysis 21/37 vs 14/19 OR: 0.47, 95%CI [0.14;1.57]¥ (p=0.22)*	1, 37 vs 19 §	Balit, 2003
No pain at 12 hours *(Secondary outcome)*		Not statistically significant: ITT analysis 30/37 vs. 18/19 OR: 0.24, 95%CI [0.03;2.10]¥ (p=0.20)*		
No delayed itchiness *(Secondary outcome)*		Not statistically significant: ITT analysis 30/37 vs 14/19 OR: 1.53, 95%CI [0.41;5.68]¥ (p=0.52)*		

Redness (total duration, hrs) *(Secondary outcome)*		Statistically significant: mITT analysis Median: 12 (IQR: 2–48) vs. 2 (IQR: 0–10 hr) (p=0.0085) In favour of *using ice pack alone* Effect size and CI cannot be calculated.		

ITT: intention to treat; IQR, interquartile range
* Calculations done by the reviewer(s) using Review Manager software
¥ Imprecision (large variability of results)
† Imprecision (lack of data)
§ Imprecision (limited sample size)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Balit, 2003	No	Yes – but shouldn't influence outcome	No	No	- Random allocation allotted a much higher percentage of people with multiple stings into the experimental group. - Outcomes were assessed by patients themselves with no reference for standardization. - Low number of participants.

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Small number of events and large variability of the results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion(s)	There is limited evidence in favour of using an ice pack alone (without topical aspirin). It was shown that topical aspirin and an ice pack resulted in a statistically significant increase of **duration of redness,** compared to an icepack alone (Balit 2003). A statistically significant decrease of **swelling, pain or itchiness**, using topical aspirin and an ice pack compared to an icepack alone, could not be demonstrated (Balit 2003). Evidence is of low quality and results of these studies are imprecise due to large variability of results and low number of events.
Reference(s)	**Articles**: Balit C.R., Isbister G.K. and Buckley N.A. *Randomized Controlled Trial of Topical Aspirin in the Treatment of Bee and Wasp Stings.* J Toxicol Clin Toxicol. 2003,41(6):801-808

Bee or wasp stings – Topical antihistamine (First aid)

Question (PICO)	Among persons with a bee/wasp sting (P), does application of topical antihistamine (I) compared to no application of topical antihistamine (C) change functional recovery, pain, complications, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the search terms: [mh "Bees"] OR [mh "Wasps"] **MEDLINE** (via PubMed interface) using the following search strategy: 1. "bee"[Mesh] OR bee [TIAB] OR "wasp"[Mesh] OR wasp [TIAB] 2. "Histamine Antagonists"[MeSH] OR antihistamine [TIAB] 3. 1 AND 2 **Embase** (via Embase.com interface) using the following search strategy: 1. 'bee sting'/exp OR 'wasp sting'/exp OR (('bee'/exp OR 'wasp'/exp OR bee*:ab,ti OR wasp*:ab,ti) AND sting*:ab,ti) 2. 'antihistaminic agent'/exp OR antihistamine:ab,ti 3. 1-2 AND
Search date	26 February 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies. **Language**: Include: English **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.

Reference(s)	/

Mosquito bite – Topical oils or repellents (Prevention)

Question (PICO)	Among adults and children (P), does the use of topical oils or repellents (I) compared to not using this (C) prevent mosquito bites (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "Culicidae"] AND [mh "Primary Prevention"] A protocol for the following Cochrane review was found: Maia 2015. Mosquito repellents for malaria prevention. The author was contacted to request the results of this review; no updated CEBaP review will be developed in the meantime, however, evidence from the 2010 CEBaP review is provisionally included below.
Search date	10 July 2015
In/Exclusion criteria	**Population**: Include: adults or children **Intervention**: Include: We included studies on insect repellents that are easily available (pharmacy or supermarket) in Belgium. These include following repellents: products containing para-menthane-diol (PMD), DEET, IR3535, icaridine (picaridine/KBR322/Bayrepel), ethyl-N-acetyl-N-butyl-beta-alaninaat, several natural repellents and oils. We only included studies comparing interventions vs control (no intervention). **Outcome**: Include: number of biting mosquitos, mortality of mosquitos **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values, studies for which it is not possible to conclude about statistical significance of results. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years (currently until 2010)

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison/Risk factor	Remarks
Uzzan, 2009, Senegal	Experimental study: randomized controlled trial (within subjects design)	100 healthy male and female volunteers catching biting mosquitos (*Anopheles*, *Culex* and *Aedes*)	1. 20% icaridine spray repellent 2. 20% para-menthane diol (PMD, major component of lemon eucalyptus oil) repellent spray 3. 50% PMD repellent spray 4. 50% DEET spray repellent 5. placebo	The following sequences, each one corresponding to a group of 20 volunteers treated during five consecutive nights was used: ABCDE, BCDEA, CDEAB,

			Each product was applied on the skin of one leg, from knee to ankle (about 15 mL of product).	DEABC and EABCD.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Number of mosquitos captured (mean/night/	50% DEET vs control	statistically significant: £† 1.25 (0-12) vs 12.5 (0-47) *In favour of 50% DEET*	1, 100 vs 100 §	Uzzan, 2009
	20% icaridine vs control	statistically significant: £† 1.43 (0-17) vs 12.5 (0-47) *In favour of 20% icaridine*		
	20% para-menthane-diol (PMD, major component of lemon eucalyptus oil) vs control	statistically significant: £† 2.37 (0-14) vs 12.5 (0-47) *In favour of 20% PMD*		
	50% para-menthane-diol	statistically significant: £† 1.29 (0-10) vs 12.5 (0-47) *In favour of 50% PMD*		

Mean (range)
£ No effect size and CI available
† Imprecision (lack of data)
§ Imprecision (limited sample size)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Uzzan, 2009	No	No	No	No	

Level of the body of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/lack of data
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion(s)	There is limited evidence in favour of DEET, icaridin and para-menthane diol. It was shown that these repellents resulted in a statistically significant increased repellency, compared to not using these (Uzzan 2009). Evidence is of low quality and results cannot be considered precise due to limited sample size and lack of data.
Reference(s)	**Articles** Uzzan B, Konate L, Diop A, Nicolas P, Dia I, Dieng Y, Izri A. *Efficacy of four insect repellents against mosquito bites: a double-blind randomized placebo-controlled field study in Senegal*. Fundam Clin Pharmacol 2009, 23(5):589-94

Mosquito bite – Wrist bands (prevention)

Question (PICO)	Among adults and children (P), does the use of wrist bands (I) compared to not using this (C) prevent mosquito bites (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Culicidae"] OR mosquito*:ti,ab,kw 2. Wristband*:ti,ab,kw or wrist band*:ti,ab,kw or bracelet*:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Culicidae"[Mesh] OR mosquito*[TIAB] OR Culicidae [TIAB] OR Culex [TIAB] 2. Wristband*[TIAB] OR wrist band*[TIAB] OR bracelet*[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'Culex'/exp OR Culicidae:ab,ti OR culex:ab,ti OR mosquito*:ab,ti 2. Wristband*:ab,ti OR (wrist NEXT/1 band*):ti,ab OR bracelet*:ab,ti 3. 1-2 AND
Search date	14 July 2015
In/Exclusion criteria	**Population**: Include: adults or children **Intervention**: Include: wristbands containing mosquito repellent (oil or insecticide) **Outcome**: Include: biting, landing, probing of mosquitoes. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Jensen, 2000, USA	Experimental: Randomised controlled trial (within subjects)	Four volunteers of which 2 used a single Repello Brand wrist band (on the right wrist), 1 used insect repellent and 1 served as the untreated negative control. The study was conducted in Trelease Woods, a University of Illinois protected woodlot in Champaign County, east central Illinois. The mosquitoes coming to the legs of volunteers	1. Repello Brand wrist band (DEET impregnated) 2. Insect repellent (Unscented Backwoods Cutter Insect Repellent) 3. Untreated negative control [data from insect repellent were not extracted] Bands were attached to the wrists of the volunteers 30 min before beginning the	

		included *Aedes triseriatus* (Say), *Aedes vexans* (Meigen), *Aedes trivitattus* (Coquillett), and *Psorophora ferox* (Humboldt).	study and were worn for 15 min indoors before driving to the study area.	
Karunamoorthi, 2009, Ethiopia	Experimental: Non-randomised controlled trial (within subjects)	Five healthy volunteers (3 males, 2 females) were recruited from the Medical Entomology Division, Vector Control Research Centre, India. Volunteer's arm were washed and cleaned with ethanol solvent. The left forearm was maintained as test and tied with repellent-treated wristband while the right forearm was tied with a wristband treated with ethanol to serve as control. The mosquitoes used for this study were *Anopheles stephensi* (Liston) and *Culex quinquefasciatus* (Say)	1. Writband containing N-N-diethyl-m-toluamide (DEET) 25% 2. Wristband containing N,N-diethyl phenylacetamide (DEPA) 25% 3. Negative control: wristband treated with ethanol Both repellents were used at two different concentrations: 1.5 and 2.0 mg/cm^3.	Laboratory study
Karunamoorthi, 2010, Ethiopia	Experimental: Non-randomised controlled trial (within subjects)	Five healthy volunteers (3 males, 2 females) were recruited from the Medical Entomology Division, Vector Control Research Centre, India. Volunteer's arm were washed and cleaned with ethanol solvent. The left forearm was maintained as test and tied with repellent-treated wristband while the right forearm was tied with a wristband treated with ethanol to serve as control. The mosquitoes used for this study were *Anopheles stephensi* and *Aedes aegypti* and *Culex quinquefasciatur*	1. Wristband containing Dimethyl phthalate (DMP) 25% at two different concentrations: 1.5 and 2.0 mg/cm^3. 2. Negative control: wristband treated with ethanol	Laboratory study
Revay, 2013, Israel	Experimental: Non-randomised controlled trial (within subjects)	8 volunteers, 5 male, 3 female professional entomologists/medics were recruited to test 7 personal protective products. Groups of 1500 female *Culex pipiens* and 1500 female *Aedes albopictus* that were 5 days old and starved for 24h were released with one species in each of two empty compartments. Volunteers were rotated through each of the 2 release chambers twice in one night for 8 consecutive nights yielding	1. OFF!® Clip-on™ Mosquito Repellent 2. Terminix® ALLCLEAR® Sidekick Mosquito Repeller 3. Evergreen products™ Super Band™ Wristband (containing geraniol oil (15%), lemongrass oil (5%) and citronella oil (2%)) 4. PIC® Citronella Plus Wristband (containing geraniol (15%), lemongrass oil (5%) and citronella oil (1%))	semi-field test

		16 repetitions for each treatment and control.	5. Sonic Insect Repeller Keychain 6. Mosquito Guard Patch 7. Mosquito Patch 8. Negative control: a volunteer that did not wear a product. [Only data on Evergreen products™ Super Band™ Wristband and PIC® Citronella Plus Wristband will be extracted]	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Numbers of mosquitoes landing	wristband vs no wristband	Statistically significant: 5.9±1.7 vs 10.5±2.1 (mean±SE) (p<0.005) *In favour of wristband*	1, 4 vs 4 § (within subjects)	Jensen, 2000
	DEET-treated wristbands (1.5 mg/cm^3) vs negative control	Statistically significant: 76 vs 823 (90.8% reduction) (p<0.001) £† *In favour of DEET-treated wristbands (1.5 mg/cm^3)*	1, 5 vs 5 § (within subjects)	Karunamoorthi, 2009
	DEET-treated wristbands (2.0 mg/cm^3) vs negative control	Statistically significant: 48 vs 966 (95.0% reduction) (p<0.001) £† *In favour of DEET-treated wristbands (2.0 mg/cm^3)*		
	DEPA-treated wristbands (1.5 mg/cm^3) vs negative control	Statistically significant: 108 vs 851 (87.3% reduction) (p<0.001) £† *In favour of DEPA-treated wristbands (1.5 mg/cm^3)*		
	DEPA-treated wristbands (2.0 mg/cm^3) vs negative control	Statistically significant: 84 vs 845 (90.1% reduction) (p<0.001) £† *In favour of DEPA-treated wristbands (2.0 mg/cm^3)*		
	DMP treated wristband (1.5 mg/cm^2) vs negative control	Statistically significant: 117 vs 844 (86.1% reduction) (p=0.0025) £† *In favour of DMP treated wristbands*	1, 5 vs 5 § (within subjects)	Karunamoorthi, 2010
	DMP treated wristband (2.0 mg/cm^2) vs negative control	Statistically significant: 174 vs 807 (78.3% reduction) (p=0.0026) £† *In favour of DMP treated wristbands*		
total number of mosquitoes biting, landing, probing	Evergreen products™ Super Band™ Wristband vs negative control	*Aedes albopictus*: Not statistically significant: 523 vs 591 (11.51% reduction) (p>0.05) £† *Culex pipiens*: Not statistically significant: 403 vs 395 (2.03% increase) (p>0.05) £†	1, 8 vs 8 §	Revay, 2013

	PIC® Citronella Plus Wristband vs negative control	*Aedes albopictus*: Not statistically significant: 698 vs 591 (18.11% increase) (p>0.05) £† *Culex pipiens*: Not statistically significant: 367 vs 395 (7.09% reduction) (p>0.05) £†		

Mean ± SD (unless otherwise indicated)
£ No SD's available, effect size and CI cannot be calculated [only if applicable for more than one cell]
¥ Imprecision (large variability of results)
§ Imprecision (limited sample size or low number of events)
† Imprecision (lack of data)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Jensen, 2000	Yes	Yes	No	No	
Karunamoorthi, 2009	Yes	Yes	No	No	
Karunamoorthi, 2010	Yes	Yes	No	No	
Revay, 2013	Unclear, not mentioned how	Yes	No	No	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/lack of data/large variability of the results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion(s)	There is limited evidence in favour of wristbands. It was shown that wristbands (treated with DEET, DEPA or DMP) resulted in a statistically significant decrease of numbers of mosquitoes landing compared to no wristbands (Jensen 2000, Karunamoorthi 2009, Karunamoorthi 2010). The mosquitoes used in these studies were *Aedes triseriatus* (Say), *Aedes vexans* (Meigen), *Aedes trivitattus* (Coquillett), *Psorophora ferox* (Humboldt), *Anopheles stephensi*, *Aedes aegypti* and *Culex quinquefasciatus*. However, a statistically significant decrease of mosquitoes landing, probing and biting using wristbands containing geraniol, lemongrass and citronella oil, compared to no wristbands, could not be demonstrated for *Culex pipiens* and *Aedes albopictus* (Revay 2013). Evidence is of low/very low quality and results cannot be considered precise due to limited sample size, lack of data and/or large variability of results.
Reference(s)	**Articles** Jensen T, Lampman R, Slamecka C, Novak RJ. *Field efficacy of commercial antimosquito products in Illinois*. Journal of the American Mosquito Control Association 2000, 16(2):148-152 Karunamoorthi K, Sabesan S. *Relative efficacy of repellent-treated wristbands against three major mosquito (Diptera: Culicidae) vectors of disease, under laboratory conditions*. International Health 2009, 1:173-177

	Revay EE, Junnila A, Xue R, Kline DL, Bernier ER, Kravchenko VD, Qualls WA, Ghattas N, Müller GC. *Evaluation of commercial products for personal protection against mosquitoes*. Acta Tropica 2013, 125(2):226-230

Mosquito bite – Oil candles (Prevention)

Question (PICO)	Among adults and children (P), does the use of oil candles (I) compared to not using this (C) prevent mosquito bites (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "Culicidae"] AND [mh "Primary Prevention"] **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Culicidae"[Mesh] OR mosquito*[TIAB] OR Culicidae [TIAB] OR Culex [TIAB] 2. Candle*[TIAB] OR bougie*[TIAB] OR taper*[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) for experimental and observational studies using the following search strategy: 1. 'Culex'/exp OR Culicidae:ab,ti OR culex:ab,ti OR mosquito:ab,ti 2. Candle*:ab,ti OR bougie*:ab,ti OR taper*:ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in MEDLINE (via PubMed interface).
Search date	19 June 2015
In/Exclusion criteria	**Population**: Include: adults or children under field conditions **Intervention**: Include: burning oil candles (geraniol, linalool, citronella) **Outcome**: Include: number of landing/biting mosquitos **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Jensen, 2000, United States	Experimental: randomized controlled trial (within subjects design)	4 volunteers taking place in a sampling station in the Trelease Woods, a University of Illinois protected woodlot in	Several anti-mosquito products were compared. For this summary the data concerning the following	2-4 mosquito collection periods were made at each collection station daily between 30 min before to 30

		Champaign County, in east central Illinois. The mosquitoes coming to the legs of volunteers included *Aedes triseriatus* (Say), *Aedes vexans* (Meigen), *Aedes trivitattus* (Coquillett), and *Psorophora ferox* (Humboldt).	comparison were extracted: 3% citronella candles vs no treatment [a positive control was also included, but data were not extracted]	min after sunset (20.15-21.15 h). The treatments were rotated to new stations each day. Landing rates were based on the number of mosquitoes landing on the exposed legs of a volunteer collector during each sampling period.
Müller, 2008a, Israel	Experimental: randomized controlled trial (within subjects design)	6 volunteers (3 male, 3 female) in Neot Ha Kikar oasis (high biting pressure) and coastal plain 10 km south of Tel Aviv (low biting pressure), Israel 14 mosquito species were found, including Culex, Anopheles and Aedes species (see paper for details).	5% geraniol candle vs not Volunteers sat in chairs, with one arm extended at 45° angle, resting on thighs, in front of them (left forearms and hands were test areas). Chairs were arranged along a line at 10 m from each other, and the volunteers rotated their positions. The candles were suspended from tripods (about 1.2 m from the ground) and were placed 1.0 m upwind from the volunteers. [data concerning protection of different oil candles, in absence of volunteers were not extracted]	Mosquitos landing, probing and biting on the arms were counted and recorded on data sheets in intervals of 5 min by the volunteers.
Müller, 2008b, Israel	Experimental: randomized controlled trial (within subjects design)	4 volunteers (2 male, 2 female) in a high biting pressure environment in Israel type of mosquitoes not mentioned	1. 5% citronella candle 2. 5% linalool candle 3. 5% geraniol candle 4. paraffin candle For the trials, the exposed legs (from knee to ankle) of each volunteer were used as a test area. On a chair (2 m from the candle) in the corner opposite the window, a person with exposed legs sat and collected landing mosquitoes for the	All mosquitos biting, probing, and landing were recorded and totaled by the volunteers. Volunteers collected the insects with an aspirator.

			following 3 h on 10 consecutive nights. [data on sand flies were not extracted]	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Landing rate (mean±SE)	3% citronella candles vs no treatment	Not statistically significant: 3.1±0.21 vs 2.6±0.24 £† (p>0.05)	1, 4 vs 4 § (within subjects)	Jensen, 2000
Average landing, probing and biting pressure per 5 min	5% geraniol candle vs not	Statistically significant: High biting pressure site: 8.14 vs 18.5 (56% reduction) £† (p<0.0001) *In favour of geraniol candles* Low biting pressure site: 2.9 vs 7.7 (62% reduction) £† (p<0.0001) *In favour of geraniol candles*	1, 6 vs 6 § (within subjects)	Müller, 2008a
Number of mosquitos caught (mean±SD)	5% citronella candle vs paraffin candle	Statistically significant: 40±10 vs 65±10 λ£† (p<0.0001) *In favour of citronella candles*	1, 4 vs 4 § (within subjects)	Müller, 2008b
	5% linalool candle vs paraffin candle	Statistically significant: 20±5 vs 65±10 λ£† (p<0.0001) *In favour of linalool candles*		
	5% geraniol candle vs paraffin candle	Statistically significant: 10±3 vs 65±10 λ£† (p<0.0001) *In favour of geraniol candles*		

† Imprecision (lack of data)
§ Imprecision (limited sample size)
£ No effect size and CI available
λ Data extracted from graph

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Jensen, 2000	Yes	yes	No	No	
Müller, 2008a	Yes	Yes	No	No	
Müller, 2008b	Yes	Yes	No	No	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/lack of data
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion(s)	**5% candles**: There is limited evidence in favour of linalool/geraniol/citronella candles. It was shown that burning these candles resulted in a statistically significantly decreased average landing, probing and biting pressure and number of mosquitos caught, compared to not using candles or paraffin candles (Müller 2008a, Müller 2008b). Evidence is of low quality and results cannot be considered precise due to limited sample size and lack of data. **3% candles**: There is limited evidence neither in favour of the intervention nor the control: a statistically significant decreased mosquito landing rate using citronella candles compared to not using these, could not be demonstrated (Jensen 2000). Evidence is of low quality and results of this study are imprecise due to limited sample size and lack of data.
Reference(s)	**Articles** Jensen T, Lampman R, Slamecka MC, Novak RJ. *Field efficacy of commercial antimosquito products in Illinois*. Journal of the American Mosquito Control Association 2000, 16:148-152 Müller GC, Junnila A, Kravchenko VD, Revay EE, Butler J, Orlova OB, Weiss RW, Schlein Y. *Ability of essential oil candles to repel biting insects in high and low biting pressure environments*. J Am Mosq Control Assoc 2008a, 24(1):154-60 Müller GC, Junnila A, Kravchenko VD, Revay EE, Butlers J, Schlein Y. *Indoor protection against mosquito and sand fly bites: a comparison between citronella, linalool, and geraniol candles*. J Am Mosq Control Assoc 2008b, 24(1):150-3

Mosquito bite – Impregnated clothing (Prevention)

Question (PICO)	Among adults and children (P), does the use of impregnated clothing (I) compared to not using this (C) prevent mosquito bites (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "Culicidae"] AND [mh "Primary Prevention"] **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Culicidae"[Mesh] OR mosquito*[TIAB] OR Culicidae [TIAB] OR Culex [TIAB] 2. "Insecticides"[Mesh] OR "Insect Repellents"[Mesh] OR repellent [TIAB] OR insecticide [TIAB] 3. "Clothing"[Mesh] OR cloth*[TIAB] OR uniform [TIAB] OR dress [TIAB] OR textile [TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) for experimental and observational studies using the following search strategy: 1. 'Culex'/exp OR Culicidae:ab,ti OR culex:ab,ti OR mosquito:ab,ti 2. 'insecticide'/exp AND 'insect repellent'/exp OR Repellent:ab,ti OR insecticide:ab,ti 3. 'clothing'/exp OR Cloth*:ab,ti OR uniform:ab,ti OR dress:ab,ti OR textile:ab,ti 4. 1-3 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in MEDLINE (via PubMed interface).
Search date	18 June 2015
In/Exclusion criteria	**Population**: Include: adults or children

	Intervention: Include: impregnated clothing, with repellents available in Europe, against Culex mosquitos which are prevalent in Europe (e.g. Culex pipiens) **Outcome**: Include: number of landing/biting mosquitos, mosquito mortality **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Fryauff, 1996, USA	Experimental: Non-randomized controlled trial	tropical weight, woodland camouflage Battle Dress Uniform (BDU) fabrics of 100% cotton were tested (not mentioned, but probably one piece per treatment group)	The uniforms were treated with an aqueous suspension of permethrin (Permanone 40% emulsifiable concentrate) to achieve a deposition rate of 0.125 mg active ingredient (AI)/cm^2 of fabric. 5 different treatment/ wash groups were compared: untreated/unwashed, treated/unwashed, treated/1-wash, treated/2-wash, treated/3-wash [only the data of the first two groups were extracted]	Prepared test fabrics were kept separately in sealed plastic bags and stored for 4-6 months at room temperature in darkness until tested; susceptibility tests with laboratory-reared mosquitoes (including Culex pipiens originating from Gharbaya, Egypt)

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Knockdown/ mortality of mosquitos	Untreated vs treated uniforms	Statistically significant: * † 1 min exposure of mosquitos to textile: -5 min post-exposure: 0% vs 15% λ -10 min post-exposure: 0% vs 30% λ -15 min post-exposure: 0% vs 49% -30 min post-exposure: 0% vs 50% λ -60 min post-exposure: 0% vs 40% λ 3 min exposure of mosquitos to textile: -5 min post-exposure: 0% vs 20% λ -10 min post-exposure: 0% vs 40% λ -15 min post-exposure: 0% vs 70% -30 min post-exposure: 0% vs 70% λ -60 min post-exposure: 0% vs 75% λ	1, 1 vs 1 § (however, not mentioned in article)	Fryauff, 1996

		5 min exposure of mosquitos to textile: -5 min post-exposure: 0% vs 30% λ -10 min post-exposure: 0% vs 60% λ -15 min post-exposure: 0% vs 75% -30 min post-exposure: 0% vs 75% λ -60 min post-exposure: 0% vs 80% λ 7 min exposure of mosquitos to textile: -5 min post-exposure: 0% vs 60% λ -10 min post-exposure: 0% vs 70% λ -15 min post-exposure: 0% vs 85% -30 min post-exposure: 0% vs 80% λ -60 min post-exposure: 0% vs 85% λ 10 min exposure of mosquitos to textile: -5 min post-exposure: 0% vs 80% λ -10 min post-exposure: 0% vs 90% λ -15 min post-exposure: 0% vs 98% -30 min post-exposure: 0% vs 90% λ -60 min post-exposure: 0% vs 90% λ *In favour of treated uniforms*		

λ Data extracted from graph

* not stated in paper, but based on significance between the 4 different wash groups

§ Imprecision (limited sample size or low number of events)

† Imprecision (lack of data)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Fryauff, 1996	No randomization (however, all uniforms were treated likewise, and no humans wearing the uniforms were involved)	Unclear (not reported if outcome assessor knew which treatment was allocated to which fabric)	No	No	Laboratory study

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Very low number of treated subjects/lack of data
Inconsistency	0	
Indirectness	-1	Laboratory study (no people wearing impregnated clothing involved)
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Conclusion(s)	There is limited evidence in favour of wearing impregnated clothes. It was shown that impregnated clothes resulted in a statistically significant increase of knockdown/mortality of Culex pipiens mosquitos, compared to non-impregnated clothes. Evidence is of very low quality and results cannot be considered precise due to limited sample size.
Reference(s)	**Articles**

	Fryauff DJ, Shoukry MA, Hanafi HA, Choi YM, Kamel KE, Schreck CE. *Contact toxicity of permethrin-impregnated military uniforms to Culex pipiens (Diptera:Culicidae) and Phlebotomus papatasi (Diptera: Psychodidae): effects of laundering and time of exposure.* J Am Mosq Control Assoc 1996, 12(1):84-90

Mosquito bite – Stagnant water (Risk factor)

Question (PICO)	In humans (P) is the presence of stagnant water (RF) compared to no presence of water (C) a risk factor for mosquito bites (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Culicidae"] OR mosquito*:ab,ti,kw OR Culex:ti,ab,kw 2. [mh "Risk Factors"] OR (risk NEXT factor*):ab,ti,kw 3. 1 AND 2 **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Culicidae"[Mesh] OR mosquito*[TIAB] OR Culicidae [TIAB] OR Culex [TIAB] 2. "Bites and Stings"[Mesh] OR bite*[TIAB] 3. "Risk Factors"[Mesh] OR risk factor*[TIAB] OR water pool[TIAB] OR stagnant water[TIAB] OR standing water[TIAB] OR swamp*[TIAB] OR lake*[TIAB] OR creek*[TIAB] OR marsh*[TIAB] OR bog*[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'Culex'/exp OR Culicidae:ab,ti OR culex:ab,ti OR mosquito:ab,ti 2. 'insect bite'/exp OR bite*:ab,ti 3. 'risk factor'/exp OR (risk NEXT/1 factor*):ab,ti OR 'water pool':ti,ab OR 'stagnant water':ti,ab OR 'standing water':ti,ab OR swamp*:ab,ti OR lake*:ab,ti OR creek*:ab,ti OR marsh*:ab,ti OR bog*:ab,ti 4. 1-3 AND
Search date	3 August 2015
In/Exclusion criteria	**Population**: Include: adults or children in Europe **Intervention (Risk factor)**: Include: stagnant water **Outcome**: Include: risk of mosquito stings, risk of malaria outcomes **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, cross-sectional surveys**,** and the data are available. Exclude: case series, animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Mosquito bite – Bednets (Prevention)

Question (PICO)	Among adults and children (P), does the use of bednets (I) compared to not using this (C) prevent mosquito bites (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "Culicidae"] AND [mh "Primary Prevention"] The following Cochrane systematic review was identified: Lengeler 2004. Insecticide-treated bed nets and curtains for preventing malaria. According to the author this systematic review will not be updated anymore because of current very strong evidence, and conducting new RCTs being considered as unethical. Therefore, only the evidence included in this review will be included. Since the Cochrane review did not include the comparison of untreated nets vs no nets, we included the evidence from the systematic review concerning bed net use in India (IFAG project, Van Remoortel 2015).
Search date	10 July 2015
In/Exclusion criteria	**Population**: Include: adults or children **Intervention**: Include: bednets **Outcome**: Include: mosquito and malaria outcomes **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Lengeler, 2004, Switzerland	Systematic review	22 studies (14 cluster RCTs and 8 individual RCTs): Trials included either the whole population of selected areas (typically in low endemicity areas) or specific age groups (typically	insecticide-treated bed nets vs no nets or untreated nets	Only studies reporting malaria outcomes were included. Only individual and cluster randomized

		children in high endemicity areas), and gender ratios were well balanced (range of male female ratio: 0.8 to 1.2) Remark: only 5 studies were included in the meta-analysis provided below (these studies included children)		controlled trials were included. Trials including only pregnant women were excluded.
Van Remoortel, 2015, Belgium	Systematic review	16 studies (7 controlled interrupted time series and 9 cluster randomised controlled trials), including 4 studies performed in low-endemic areas (annual parasite incidence ≤2) and 12 studies in high-endemic areas (annual parasite incidence >2) in India Remark: only 14 studies were included in the meta-analysis provided below	1. treated bednets 2. untreated bednets 3. no nets [only data from the comparison untreated bednets vs no nets were extracted since the other comparison was already covered by the Cochrane systematic review (Lengeler 2004)]	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Child mortality from all causes	Treated vs untreated nets	Statistically significant: RR: 0.77, 95%CI [0.63; 0.95] *In favour of treated nets*	1, 11864 vs 12988	Lengeler, 2004
	Treated nets vs no nets	Statistically significant: RR: 0.83, 95%CI [0.76; 0.90] *In favour of treated nets*	4, 62659 vs 61710	
Parasite prevalence	Untreated nets vs no nets	Statistically significant: High endemic areas: 1328/15963 vs 1720/14423 RR: 0.70, 95%CI [0.56;0.87] *In favour of untreated nets*	10, 15963 vs 14423	Van Remoortel, 2015
		Statistically significant: Low endemic areas: 51/6115 vs 105/5257 RR: 0.49 95%CI [0.28;0.84] *In favour of untreated nets*	4, 6115 vs 5257	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See systematic reviews
Imprecision	0	
Inconsistency	0	
Indirectness	0	We did not downgrade for indirectness, although these systematic reviews did not report the outcome of interest in our PICO (however, if statistically significant effects on malarial outcomes are found, an effect will also be present for mosquito outcomes)
Publication bias	0	
QUALITY (GRADE)	**Final grading Moderate [B]**	

Conclusion(s)	There is evidence in favour of using treated or untreated bednets. It was shown that (un)treated bednets resulted in a statistically significant decrease of child mortality compared to untreated nets or not using a bednet (Lengeler 2004, Van Remoortel 2015). Evidence is of moderate quality.
Reference(s)	**Systematic reviews** Lengeler C. *Insecticide-treated bed nets and curtains for preventing malaria*. Cochrane Database of Systematic Reviews 2004, Issue 2 Van Remoortel H, De Buck E, Singhal M, Vandekerckhove P, Agarwal SP. *Effectiveness of insecticide-treated and untreated nets to prevent malaria in India*. Trop Med Int Health 2015, 20(8):972-82

Mosquito bite – Mosquito coils (Prevention)

Question (PICO)	Among adults and children (P), does the use of mosquito coils (I) compared to not using this (C) prevent mosquito bites (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "Culicidae"] AND [mh "Primary Prevention"] **MEDLINE** (via PubMed interface) for existing systematic reviews, using the following search strategy: 1. "Culicidae"[Mesh] OR mosquito*[TIAB] OR Culicidae [TIAB] OR Culex [TIAB] 2. Coil*[TIAB] 3. ((((((((((Meta-Analysis as Topic[Mesh])) OR ((meta analy*[TIAB]))) OR ((metaanaly*[TIAB]))) OR ((Meta-Analysis[Publication Type]))) OR ((systematic review*[TIAB] OR systematic overview*[TIAB]))) OR ((Review Literature as Topic[Mesh])))) OR ((cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB]))) OR ((reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB]))) OR ((((selection criteria[TIAB] OR data extraction[TIAB])) AND ((Review[PT]))))) NOT ((Comment[PT] OR Letter[PT] OR Editorial[PT] OR animal[Mesh] NOT (animal[Mesh] AND human[Mesh]))) 4. 1-3 AND An update of an existing systematic review was made, using the following search strategy: **MEDLINE** (via PubMed interface): 1. "Culicidae"[Mesh] OR mosquito*[TIAB] OR Culicidae [TIAB] OR Culex [TIAB] 2. Coil*[TIAB] 3. 1 AND 2 Limits 2011-2015 **Embase** (via Embase.com interface): 1. 'Culex'/exp OR Culicidae:ab,ti OR culex:ab,ti OR mosquito:ab,ti 2. Coil*:ab,ti 3. 1-2 AND Limits 2011-2015 Systematic review, retrieved with the above searches, and used as source for individual studies: Ogoma, 2012
Search date	9 July 2015
In/Exclusion criteria	**Population**: Include: adults or children **Intervention**: Include: mosquito coils vs no mosquito coils

	Outcome: Include: prevention of mosquito stings under field conditions, including studies taking place in experimental huts with wild mosquitos or mosquitos released outside the hut (different types of mosquitos) Exclude: studies measuring mosquito outcomes under laboratory conditions; studies in semi-field conditions with laboratory reared mosquitos in cages. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Achee, 2012, USA	Experimental: non-randomized controlled trial (within subjects design)	6 collectors were spread over 3 experimental huts of 50 m^3 in Pu Tuey Village, Kanchanaburi Province, Thailand. Test cohorts of 100 female, 4–7 day old, 24 h sugar-starved *Aedes aegypti* mosquitoes were uniquely marked and simultaneously released from fixed positions 10 m outside of each hut.	1. 0.00625% metofluthrin coils 2. no coil 3. blank coil (coil without active ingredient) [data on the blank coil were not extracted] During each experimental day, the coil was placed within a 2 cm X 30 cm enamel bowl positioned on the floor at the center of the experimental huts. Coils were lit as soon as mosquitos were released and were replaced with a second coil after 6 h of burn time. Collector teams were rotated among huts each day at 12.00 h.	Interception traps were sampled for entering mosquitoes using manual aspiration every 20 min. The total number of *Ae. aegypti* collected from interception traps affixed to experimental huts was used to calculate percent reduction in *Ae. aegypti* entry (i.e., deterrency)
Ogoma, 2012, Tanzania	Systematic review	17 studies, no specific description of population in the studies provided	Mosquito coils vs no mosquito coils	Only laboratory and field studies that quantified mosquito responses including biting/feeding inhibition of mosquitoes, knock-down time and percentage mortality

				24 hours post-exposure to insecticides, deterrence, repellency or irritancy of insecticides were included. Studies where the dose of active ingredient was not indicated were excluded. All studies where coils contained a mixture of insecticides or additives were excluded.
Ogoma, 2014, Tanzania	Experimental: randomized controlled trial (within subjects design)	8 male volunteers were spread over 4 experimental huts of 6.5 m x 3.5 m x 2.5 m in the Kilombero valley in the South East of Tanzania with with wild Anopheles arabiensis mosquitoes	1. 0.03% Transfluthrin coils 2. 0.00625% Metofluthrin coils 3. DDT sprayed on palm woven mats to fit on walls 4. no insecticide [data on DDT were not extracted] The treatments were tested for four nights per week and were rotated weekly. Two coils were placed on the floor in the middle of the hut at the start of the experiment and they were replaced with new ones when they burned out.	Half of the eaves and all of the windows were fitted with exit traps suspended outside the huts to trap those mosquitoes that attempt to leave.

Synthesis of findings

The studies included in the systematic review did not fulfill our selection criteria (only 1 study was performed in field conditions, however this study (Smith, 1972) was unavailable.

Outcome	**Comparison**	**Effect Size**	**#studies, # participants**	**Reference**
% mosquito knock down	Metofluthrin coil vs no coil	Not statistically significant: 4/240 vs 0/60 RR: 2.28, 95%CI [0.12;41.74] * ¥ (p=0.58)	1, 6 vs 6 § (within subjects design)	Achee, 2012
Indoor mosquito densities		Not statistically significant: *Culex quinquefasciatus* RR: 0.72, 95%CI [0.61;0.85] (p=0.143)	1, 8 vs 8 § (within subjects design)	Ogoma, 2014
	Transfluthrin coils vs no coil	Statistically significant: *Culex quinquefasciatus* RR: 0.87, 95% CI [0.73;1.05]		

		(p<0.001) *In favour of transfluthrin coil*		

* Calculations done by the reviewer(s) using Review Manager software
§ Imprecision (limited sample size or low number of events)
¥ Imprecision (large variability of results)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Achee, 2012	Yes, not randomized	Not possible for no coil group	No	No	
Ogoma, 2014	No (treatments randomly allocated to huts)	Not possible for no coil group	No	No	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Very low number of treated subjects
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	**Metofluthrin coil**: There is limited evidence neither in favour of a metofluthrin coil nor the control. A statistically significant increase of the percentage of mosquito knock down and decrease of indoor mosquito densities using a metofluthrin coil compared to not using a coil could not be demonstrated (Achee 2012, Ogoma 2014). Evidence is of low quality and results of these studies are imprecise due to limited sample size and large variability of results. **Transfluthrin coils**: There is limited evidence in favour of using transfluthrin coils. It was shown that transfluthrin coils resulted in a statistically significant decrease of indoor mosquito densities, compared to not using a coild (Ogoma 2014). Evidence is of low quality and results of these studies are imprecise due to limited sample size.
Reference(s)	**Articles** Achee N, Masuoka P, Smith P, Martin N, Chareonviryiphap T, Polsomboon S, Hendarto J, Grieco J. *Identifying the effective concentration for spatial repellency of the dengue vector Aedes aegypti*. Parasit Vectors. 2012, 5:300 Ogoma SB, Lorenz LM, Ngonyani H, Sangusangu R, Kitumbukile M, Kilalangongono M, Simfukwe ET, Mseka A, Mbeyela E, Roman D, Moore J, Kreppel K, Maia MF, Moore SJ. *An experimental hut study to quantify the effect of DDT and airborne pyrethroids on entomological parameters of malaria transmission*. Malar J 2014, 13:131 **Systematic reviews** Ogoma SB, Moore SJ, Maia MF. *A systematic review of mosquito coils and passive emanators: defining recommendations for spatial repellency testing methodologies.* Parasit Vectors 2012, 5:287

Bee or wasp stings – Sweet odor (Risk factor)

Question (PICO)	In adults and children (P), is a sweet odor (I) compared to no sweet odor (C) a risk factor for getting a bee or wasp sting?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the search terms: [mh "Bees"] OR [mh "Wasps"] **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Bees"[Mesh] OR bee*[TIAB] OR "Wasps"[Mesh] OR wasp*[TIAB] 2. "Bites and Stings"[Mesh] OR sting*[TIAB] 3. "Odors"[Mesh] OR "Perfume"[Mesh] OR "Smell"[Mesh] OR sweet [TIAB] OR smell [TIAB] OR odor [TIAB] OR perfume [TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'bee sting'/exp OR 'wasp sting'/exp OR (('bee'/exp OR 'wasp'/exp OR bee*:ab,ti OR wasp*:ab,ti) AND sting*:ab,ti) 2. 'odor'/exp OR 'fragrance'/exp OR sweet:ti,ab OR smell:ti,ab OR odor:ti,ab OR perfume:ti,ab 3. 1-2 AND
Search date	12 June 2015
In/Exclusion criteria	**Population**: Include: people or healthy volunteers with a bee/wasp sting **Intervention**: Include: sweet odor or perfume **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies. **Language**: Include: English **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion(s)	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	Not applicable

Bee, wasp or mosquito stings – Coloured clothing (Risk Factor)

Question (PICO)	In healthy people (P), is wearing coloured clothing (RF) compared to not wearing coloured clothing (C) a risk factor for bee, wasp or mosquito stings (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Bees"] OR [mh "Wasps"] OR bee:ti,ab,kw OR wasp*:ti,ab,kw OR [mh "Culicidae"] OR mosquito*:ti,ab,kw 2. [mh "clothing"] OR cloth*:ti,ab,kw OR uniform*:ti,ab,kw OR textile*:ti,ab,kw OR garment*:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies and systematic reviews using the following search strategy: 1. "bees"[MeSH] OR "wasps"[MeSH] OR "bee*"[TIAB] OR "wasp*"[TIAB] OR "culicidae"[MeSH] OR "mosquito*"[TIAB] 2. "clothing"[MeSH] OR "cloth*"[TIAB] OR "uniform*"[TIAB] OR "textile*"[TIAB] OR "garment*"[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'bee'/exp OR bee*:ab,ti OR 'wasp'/exp OR wasp*:ab,ti OR 'mosquito'/exp OR mosquito*:ab,ti 2. 'clothing'/exp OR cloth*:ab,ti OR uniform*:ab,ti OR textile*:ab,ti OR garment*:ab,ti 3. 'bites and stings'/exp OR sting*:ab,ti OR bite*:ab,ti 4. 1-3 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in MEDLINE (via PubMed interface).
Search date	8 February 2016
In/Exclusion criteria	**Population:** Include: Healthy people. **Intervention:** Include: Wearing coloured clothing. Exclude: Wearing impregnated clothing. **Comparison:** Include: Not wearing coloured clothing. **Outcome:** Include: The prevalence of bee/wasp/mosquito stings. **Study design:** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: observational studies if intervention is already included in experimental studies, case series, cross-sectional studies, animal studies, ex vivo or in vitro studies, conference abstracts unless no other relevant data is available, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Risk factor	Remarks
Silva, 2013, Portugal	Observational: Case-control study	61 cases (people stung by bee or wasp), aged 45 IQR[28-65] and 61 controls (people witnessing the stung but not stung), aged 46 IQR[36-52].	Risk factors for getting stung: Gender; being in motion vs standing still; shorts pants/dresses vs long pants; long sleeved shirt vs short sleeved shirt; open shoes/bare feet vs closed shoes; dark clothing vs bright/white clothing; use of perfume vs no use of perfume. [Only data from dark clothing vs bright/white clothing was extracted]	

Synthesis of findings

Outcome	Risk factor	Effect Size	#studies, # participants	Reference
Getting stung by a bee/wasp	Dark clothes vs bright/white clothes	Not statistically significant: 24/45 vs 24/37 RR: 0.82, 95%CI [0.57;1.18] *¥ (p=0.29)	1, 45 vs 37 §	Silva, 2013

* Calculations done by the reviewer(s) using Review Manager software

¥ Imprecision (large variability of results)

§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations
Silva, 2013	No	Yes, questionnaires regarding clothing at an event that might have taken place 3 years ago seem very prone to recall bias, especially when considering the controls.	Yes, univariate analysis.	Yes, outcome measurement only done on 45 vs 37, while 61 cases and controls were eligible to participate.	Conference poster

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample size/large variability of results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Conclusion	There is limited evidence neither for the benefit/harm of wearing dark coloured clothes nor wearing light/bright coloured clothes. A statistically significant increased risk of bee/wasp stings in case of wearing dark coloured clothes compared to wearing light/bright coloured clothes could not be demonstrated (Silva, 2013).

	Evidence is of very low quality and results of this study are imprecise due to limited sample size and large variability of results.
Reference(s)	**Articles** Silva D, Santos N, Pereira A, Pereira AM, Delgado L, Coimbra A. *Risk factors for hymenoptera stings-a case-control study.* Allergy: European Journal of Allergy and Clinical Immunology 2013 68 SUPPL. 97 (491-492)

Tick bite – Removal with forceps (First aid)

Question (PICO)	Among persons with a tick bite (P), does removal by twisting with forceps (I) compared to pulling with forceps (C) increase the chance on complete removal of the tick, change functional recovery, pain, complications, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search term: [mh "Ticks"] **MEDLINE** (via PubMed interface) using the following search strategy: "Ticks" [Mesh] AND remov*[TIAB] **Embase** (via Embase.com interface) using the following search strategy: 'tick'/exp AND ('remove':ab:ti OR 'removal':ab:ti OR 'removing':ab:ti) BestBET used as source for individual studies: Teece, 2002, The straight, slow method may be best for removing ticks.
Search date	19 February 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. We included animal studies. Exclude: case series, cross-sectional studies, ex vivo or in vitro studies. **Language**: Include: English **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
De Boer 1993, The Netherlands	Experimental: non-randomized controlled trial	1060 ticks (*Ixodes Ricinus*) applied on four pigs and 356 ticks on two sheep 218 nymphs and 59 females attached on pigs; 6 nymphs and 27 females attached on sheep	Removal by pulling or removal by rotation using a blunt forceps	Scoring of damaged mouth parts: Missing portions of the hypostome, chelicerae, and capitulum were estimated separately. For each, the range of missing parts was 0-1; a score of 1 was given if the entire portion was missing.
Needham, 1985, USA	Experimental: non-randomized controlled trial	29 American dog ticks (*Dermacentor variabilis);* 22 lone star ticks (*Amblyomma Americanum)* attached on the back of a female Dorset sheep; attachment to the host for 72-96 hours or 12-15 hours.	Removal by (1) pulling straight up with steady even pressure; (2) pulling straight up with a quick motion; (3) pulling the tick parallel with the skin using a steady even pressure (ventral aspect of the tick up); (4) twisting clockwise (two to three revolutions); using forceps	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Number of ticks with damaged mouthparts	Pulling with blunt forceps vs rotation with blunt forceps	<u>Statistically significant:</u> 99/224 vs 70/87 RR: 0.55, 95%CI [0.46;0.66] (p<0.00001) *In favour of pulling* The effect size and p-value was calculated by the reviewer using the Review Manager Software	1, 224 vs 87 §	De Boer, 1993
Number of ticks with damaged mouthparts	(1) pulling straight up with a quick motion with forceps (2) pulling straight up with steady pressure with forceps (3) pulling parallel with the skin with forceps vs	Not statistically significant: (1) vs (4): 7/7 vs 5/5 RR: 1.0, 95%CI [0.74;1.35]¥ (p=1.0) (2) or (3) vs (4): 5/5 vs 5/5 5/5 vs 5/5	1, 7 vs 5 vs 5 vs 5 §	Needham, 1985

	(4) twisting clockwise with forceps	RR: 1.0, 95%CI [0.71; 1.41]¥ (p=1.0) The effect size and p-value was calculated by the reviewer using the Review Manager Software		
Number of ticks with mouthparts that broke off	(1) pulling straight up with a quick motion (2) pulling straight up with steady pressure (3) pulling parallel with the skin vs (4) twisting clockwise	Not statistically significant: (1) vs (4): 7/7 vs 0/5 RR: 11.25, 95%CI [0.79;160.81] (p=0.07) (2) or (3) vs (4): 5/5 vs 0/5 5/5 vs 0/5 RR: 11.0, 95%CI [0.77;158.01]¥ (p=0.08) The effect size and p-value was calculated by the reviewer using the Review Manager Software	1, 7 vs 5 vs 5 vs 5 §	Needham, 1985

¥ Imprecision (large variability of results)
† Imprecision (lack of data)
§ Imprecision (limited sample size)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
De Boer, 1993	yes	yes	no	no	Sections of the skin rather than individual ticks were treated with the chemicals, because the ticks often attached in clusters. Ticks receiving different treatments were not randomized.
Needham, 1985	yes	yes	no	no	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Small number of events, data lacking, large variability in results
Inconsistency	0	
Indirectness	-1	Animal studies
Publication bias	0	
QUALITY (GRADE)	**Final grading Very Low [D]**	

Conclusion(s)	Needham 1985 indicates that species differences affect the outcome of forcible tick removal. The *Ixodes ricinus* is mainly present in Europe. There is limited evidence in favour of pulling with forceps compared to rotation with forceps to remove a tick.

	It was shown in one study that pulling with forceps resulted in a statistically significant decrease of ticks with damaged mouthparts, compared to rotating with forceps (De Boer 1993). In one smaller study was shown that pulling did not result in a statistically significant decrease of damaged tick mouthparts, compared to rotating (Needham 1985). Evidence is of very low quality and results of these studies are imprecise due to limited sample size and large variability of results.
Reference(s)	**Articles** De Boer R, van den Bogaard AE. *Removal of attached nymphs and adults of Ixodes ricinus (Acari: Ixodidae).* J Med Entomol. 1993, 30(4):748-752. Duscher GG, Peschke R, Tichy A. *Mechanical tools for the removal of Ixodes ricinus female ticks – differences of instruments and pulling or twisting?* Parasitol. Res. 2012, 111:1505-1511. Needham GR. *Evaluation of five popular methods for tick removal.* Pediatrics 1985, 75(6):997-1002. Zenner L, Devron-Gaillot E, Callait-Cardinal MP. *Evaluation of four manual tick-removal devices for dogs and cats.* Vet Rec. 2006, 159(16):526-529.

Tick bite – Removal with specialized devices (First aid)

Question (PICO)	Among persons with a tick bite (P), does removal with a specialized device (I) compared to another specialized device (C) increase the chance on complete removal of the tick, change functional recovery, pain, complications, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search term: [mh "Ticks"] **MEDLINE** (via PubMed interface) using the following search strategy: "Ticks" [Mesh] AND remov*[TIAB] **Embase** (via Embase.com interface) using the following search strategy: 'tick'/exp AND ('remove':ab:ti OR 'removal':ab:ti OR 'removing':ab:ti) BestBET used as source for individual studies: Teece, 2002, The straight, slow method may be best for removing ticks.
Search date	19 February 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available.

	An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. We included animal studies. Exclude: case series, cross-sectional studies, ex vivo or in vitro studies. **Language**: Include: English **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Duscher, 2012, Austria	Experimental: non-randomized controlled trial	596 ticks: 541 *Ixodes ricinus*, 40 *Ixodes hexagonus;* 2 *Haemaphysalis concinna;* 1 *Dermacentor reticulates;* 1 *Rhipicephalus sanguineus;* 11 undefined, attached to 320 dogs, 198 cats, 6 hedgehogs, 1 guinea pig, 2 undefined hosts.	Removal by (1) twisting with pen-tweezers, (2) twisting with a tick twister, (3) twisting with Lasso (Trix tick remover), (4) pulling with forceps, (5) pulling with card (TickPic)	Scoring of condition of mouth parts: 1= intact, 4= totally severed
Zenner, 2006, France	Experimental: non-randomized controlled trial	236 ticks attached to 178 dogs and 46 cats; identified as 193 long hypostome species (*Ixodes ricinus*), 43 short hypostome species (30 *Dermacentor reticulatus* and 13 *Rhipicephalus sanguineus*).Ticks were removed by veterinarians or pet owners.	Removal by: (1) pulling with a small surgical forceps with straight, very sharp jaws (Adson forceps). Grab the tick close to its implantation site and pull the tick parallel with the skin; (2) pulling with Pro-Tick Remedy (scs). It has a metal spatula with a pointed end that has a slit of 9 mm that narrows progressively. Place the slit around the mouthparts of the tick and apply traction at 90° to the surface of the skin to extract it; (3) rotating with Pen-Tweezers (Buster), it has two opposing jaws that open when a button is depressed and close when it is released; (4) rotating Crochet O'Tom (H3D), with a hook with a slit at the end. Place the slit around the mouthparts and rotate.	Scoring of condition of mouth parts: 1= intact, 4= totally severed

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Condition of tick's mouthparts (removal by veterinarian)	Pulling with surgical forceps vs Rotating with hook with slip	Statistically significant: Data in figures. No raw data available, effect† size and CI cannot be calculated.	Not indicated in article	Zenner, 2006

		(p<0.01) *in favour of rotating*		
Condition of tick's mouthparts (removal by pet owner)	Pulling with Pro-Tick Remedy vs Rotating with Pen-Tweezers vs Rotating with hook with slip	<u>Statistically significant:</u> Data in figures. No raw data available, effect† size and CI cannot be calculated. (p<0.01) *in favour of rotating with hook.*	Not indicated in article	Zenner, 2006
Condition of tick's mouthparts (female *I. ricinus*)	(1) twisting with pen-tweezers (2) twisting with a tick twister (3) twisting with Lasso (4) pulling with forceps (5) pulling with card	<u>Statistically significant:</u> No raw data available, effect† size and CI cannot be calculated. (1) vs (3): p=0.03 in *favour of pen-tweezer* (2) vs (3): p=0.03 (2) vs (4): p<0.01 *in favour of tick twister* (3) vs (5): p=0.02 *in favour of Lasso* Not statistically significant: No raw data available, effect† size and CI cannot be calculated. (1) vs (2): p=0.07 (1) vs (4): p=0.36 (1) vs (5): p=0.36 (2) vs (5): p=0.72 (3) vs (4): p=0.64 (4) vs (5): p=0.06	Not indicated in article	Duscher, 2012
Time required to remove tick (removal by veterinarian)	Pulling with surgical forceps vs Rotating with hook with slip	<u>Statistically significant:</u> Data in figures. No raw data available, effect† size and CI cannot be calculated. (p<0.05) *in favour of rotating*	Not indicated in article	Zenner, 2006
Time required to remove tick (removal by pet owner)	Pulling with Pro-Tick Remedy vs Rotating with Pen-Tweezers vs Rotating with hook with slip	<u>Statistically significant:</u> Data in figures. No raw data available, effect† size and CI cannot be calculated. (p<0.05) *in favour of rotating with hook*	Not indicated in article	Zenner, 2006
Ease with which tick was grabbed (removal by veterinarian)	Pulling with surgical forceps vs Rotating with hook with slip	<u>Statistically significant:</u> Data in figures. No raw data available, effect† size and CI cannot be calculated. (p<0.05) *in favour of rotating*	Not indicated in article	Zenner, 2006
Ease with which tick was grabbed (removal by pet owner)	Pulling with Pro-Tick Remedy vs Rotating with Pen-Tweezers vs Rotating with hook with slip	<u>Statistically significant:</u> Data in figures. No raw data available, effect† size and CI cannot be calculated.	Not indicated in article	Zenner, 2006

		(p<0.05) *in favour of rotating with hook*		
Force needed to extract tick (removal by veterinarian)	Pulling with surgical forceps vs Rotating with hook with slip	Statistically significant: Data in figures. No raw data available, effect† size and CI cannot be calculated. (p<0.01) *in favour of rotating*	Not indicated in article	Zenner, 2006
Force needed to extract tick (removal by pet owner)	Pulling with Pro-Tick Remedy vs Rotating with Pen-Tweezers vs Rotating with hook with slip	Statistically significant: Data in figures. No raw data available, effect† size and CI cannot be calculated. (p<0.01) *in favour of rotating with hook*	Not indicated in article	Zenner, 2006

¥ Imprecision (large variability of results)
† Imprecision (lack of data)
§ Imprecision (limited sample size)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Duscher, 2012	yes	yes	Unclear (no raw data are given)	no	The study was performed by different veterinarians, including several tick species, this can lead to different performances and interpretations of results.
Zenner, 2006	no	yes	Unclear (no raw data are given)	no	The study was performed in 18 different veterinarian clinics, including several tick species, this can lead to different performances and interpretations of results.

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Small number of events, data lacking, large variability in results
Inconsistency	0	
Indirectness	-1	Animal studies
Publication bias	0	
QUALITY (GRADE)	**Final grading Very Low [D]**	

Conclusion(s)	There is limited evidence in favour of rotating with a hook with slip (commercial O'Tom Tick) to remove a tick. It was shown in one study that rotating with a hook with slip resulted in a statistically significant decrease of **damaged tick mouthparts**, time to remove tick, ease with which tick is grabbed, force needed to extract tick compared to pulling with surgical forceps, or pulling with Pro-Tick Remedy or rotating with Pen-Tweezers (Zenner 2006). In a second study it was shown that rotating with a hook with slip (Tick Twister) resulted in a statistically significant decrease of **damaged tick mouthparts**, compared to twisting with a Lasso or pulling with forceps (Duscher 2012). No statistically

	significant difference could be demonstrated when comparing the Tick Twister with Pen-Tweezers or a card (TickPic). Evidence is of very low quality and results of these studies are imprecise due to a lack of data. However, a statistically significant decrease of **failure to remove the tick**, by rotating with a hook with slip compared to pulling with surgical forceps, pulling with Pro-Tick Remedy or rotating with Pen-Tweezers, could not be demonstrated (Zenner 2006). Evidence is of very low quality and results of these studies are imprecise due to a lack of data.
Reference(s)	**Articles** Duscher GG, Peschke R, Tichy A. *Mechanical tools for the removal of Ixodes ricinus female ticks – differences of instruments and pulling or twisting?* Parasitol. Res. 2012, 111:1505-1511. Zenner L, Devron-Gaillot E, Callait-Cardinal MP. *Evaluation of four manual tick-removal devices for dogs and cats.* Vet Rec. 2006, 159(16):526-529.

Tick bite – Removal by chemical treatment or heat (First aid)

Question (PICO)	Among persons with a tick bite (P), does chemical treatment or heat (I) compared to no/other chemical treatment or heat (C) increase the chance on complete removal of the tick, self-detachment, change functional recovery, pain, complications, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search term: [mh "Ticks"] **MEDLINE** (via PubMed interface) using the following search strategy: "Ticks" [Mesh] AND remov*[TIAB] **Embase** (via Embase.com interface) using the following search strategy: 'tick'/exp AND ('remove':ab:ti OR 'removal':ab:ti OR 'removing':ab:ti) BestBET used as source for individual studies: Teece, 2002, The straight, slow method may be best for removing ticks.
Search date	19 February 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available.

	An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. We included animal studies. Exclude: case series, cross-sectional studies, ex vivo or in vitro studies. **Language**: Include: English **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
De Boer 1993, The Netherlands	Experimental: non-randomized controlled trial	1060 ticks (*Ixodes Ricinus*) applied on four pigs and 356 ticks on two sheep 218 nymphs and 59 females attached on pigs;6 nymphs and 27 females attached on sheep 130 nymphs and 45 females were treated	Removal (<24h or 72h) after application of gasoline or methylated spirit on a wad or cotton wool or nail polish (30-60min)	Scoring of damaged mouth parts: Missing portions of the hypostome, chelicerae, and capitulum were estimated separately. For each, the range of missing parts was 0-1; a score of 1 was given if the entire portion was missing.
Needham, 1985, USA	Experimental: non-randomised controlled trial	29 American dog ticks (*Dermacentor variabilis);* 22 lone star ticks (*Amblyomma Americanum)* attached on the back of a female Dorset sheep; attachment to the host for 72-96 hours or 12-15 hours.	Treatment with (1) a generous amount of petroleum jelly applied to dorsum and venter, making certain that the spiracles (respiratory openings) were covered; (2) similar treatment with clear fingernail polish; (3) 70% isopropyl alcohol applied to the dorsum and venter with a cotton swab; and (4) a wooden kitchen match was struck, allowed to burn until red hot, then blown out, and immediately held to the dorsum of the tick for 5 to 10 seconds.	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Number of nymphs with damaged mouthparts after	Chemical treatment (1)gasoline (2)methylated spirit (3)nail polish	Not statistically significant: (1) vs (4) 11/44 vs 10/29 RR: 0.72, 95%CI [0.35;1.48]¥	1, (1) 44 vs 29 (2) 52 vs 29 (3) 34 vs 29	De Boer, 1993

removal, <24h attachment	vs (4)no treatment	(p=0.38)* (2) vs (4) 27/52 vs 10/29 RR: 1.51, 95%CI [0.86;2.65]¥ (p=0.16)* (3) vs (4) 15/34 vs 10/29 RR: 1.28, 95%CI [0.68;2.40]¥ (p=0.44)*	§ 	
Number of females with damaged mouthparts after removal, 72h attachment	Chemical treatment (1)gasoline (2)methylated spirit (3)nail polish vs (4)no treatment	Not statistically significant: (1) vs (4) 20/28 vs 36/41 RR: 0.81, 95%CI [0.36;1.06]¥ (p=0.12)* (2) vs (4) 4/5 vs 36/41 RR: 0.91, 95%CI [0.58;1.43]¥ (p=0.69)* <u>Statistically significant:</u> (3) vs (4) 5/12 vs 36/41 RR: 0.47, 95%CI [0.24;0.94]¥ (p=0.03)* *In favour of nail polish*	1, (1) 28 vs 41 (2) 5 vs 41 (3) 12 vs 41 §	De Boer, 1993
Number of ticks 'self-detached' (within 2h) after 72-96h attachment	Chemical treatment (1) petroleum jelly (2) clear fingernail polish (3) 70% isopropyl alcohol (4) hot kitchen match	Not statistically significant: (1) 0/10 (2) 0/4 (3) 0/4 (4) 0/4 £	1, 10 vs 4 vs 4 vs 4 §	Needham, 1985
Number of ticks 'self-detached' (within 2h) after 12-15h attachment	Chemical treatment (1) petroleum jelly (2) clear fingernail polish (3) 70% isopropyl alcohol (4) hot kitchen match	Not statistically significant: (1) 0/4 (2) 0/4 (3) 0/4 (4) 0/4 £	1, 4 vs 4 vs 4 vs 4 §	Needham, 1985
Number of females with damaged mouthparts after removal with forceps, 72-96h attachment	Chemical treatment (petroleum jelly, clear fingernail polish, 70% isopropyl alcohol, or hot kitchen match) vs No treatment	Not statistically significant: 0/22 vs 0/5 £	1, 22 vs 5 §	Needham, 1985
Number of females with damaged mouthparts after removal with forceps, 12-15h attachment	Chemical treatment (petroleum jelly, clear fingernail polish, 70% isopropyl alcohol, or hot kitchen match) vs No treatment	Not statistically significant: 0/16 vs 0/4 £	1, 16 vs 4 §	Needham, 1985

* Calculations done by the reviewer(s) using Review Manager software

£ No effect size/CI available

¥ Imprecision (large variability of results)
† Imprecision (lack of data)
§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
De Boer, 1993	yes	yes	no	no	Sections of the skin rather than individual ticks were treated with the chemicals, because the ticks often attached in clusters. Ticks receiving different treatments were not randomized.
Needham, 1985	yes	yes	no	no	Several tick species were included in the study.

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Low number of events
Inconsistency	0	
Indirectness	-1	Animal studies
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Conclusion(s)	Needham 1985 indicates that species differences affect the outcome of forcible tick removal. The *Ixodes ricinus* is mainly present in Europe. **Different chemicals or heat** (gasoline, methylated spirit, petroleum jelly, 70% isopropyl alcohol, or a hot kitchen match): There is limited evidence neither in favour of the intervention (using chemicals) nor the control (no treatment). A statistically significant decrease of damaged mouthparts and increase of self-detachment could not be demonstrated when ticks were mechanical removed, after chemical treatment with gasoline, methylated spirit, petroleum jelly, 70% isopropyl alcohol, or a hot kitchen match (De Boer 1993, Needham 1985). Evidence is of very low quality and results of these studies are imprecise due to large variability of results or low number of events. **Nail polish:** There is conflicting evidence from 2 experimental studies. In one small study, a statistically significant decrease of damaged mouthparts could not be demonstrated when ticks were mechanical removed, after chemical treatment with nail polish (Needham 1985). In another study it was shown that using nail polish resulted in a statistically significant decrease of damaged tick mouthparts after mechanical removal compared to no chemical treatment with nail polish (De Boer 1993). The conflicting evidence could be caused by the different tick species used in the included papers. Evidence is of very low quality and results of these studies are imprecise due to large variability of results or low number of events.
Reference(s)	**Articles** De Boer R, van den Bogaard AE. *Removal of attached nymphs and adults of Ixodes ricinus (Acari: Ixodidae).* J Med Entomol. 1993, 30(4):748-752.

	Needham GR. *Evaluation of five popular methods for tick removal.* Pediatrics 1985, 75(6):997-1002.

Tick bite – Specialized clothing (Prevention)

Question (PICO)	Among adults and children (P), does the use of specialised clothing (I) compared to not using this (C) prevent tick bites (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Ticks"] OR [mh "Tick Control"] OR [mh "Tick Bites"] OR tick*:ti,ab,kw 2. [mh "Clothing"] OR (uniform):ti,ab,kw OR (dress):ti,ab,kw OR (textile):ti,ab,kw OR cloth*:ti,ab,kw 3. 1 AND 2 **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Ticks"[Mesh] OR tick*[TIAB] 2. "Bites and Stings"[Mesh] OR bite*[TIAB] 3. 1 AND 2 4. "Tick Bites"[Mesh] 5. 3 OR 4 6. "Clothing"[Mesh] OR cloth*[TIAB] OR uniform [TIAB] OR dress [TIAB] OR textile [TIAB] 7. 5 AND 6 **Embase** (via Embase.com interface) for experimental and observational studies using the following search strategy: 1. 'tick'/exp OR tick*:ab,ti 2. 'bites and stings'/exp OR bite*:ab,ti 3. 1 AND 2 4. 'tick bite'/exp 5. 3 OR 4 6. 'clothing'/exp OR Cloth*:ab,ti OR uniform:ab,ti OR dress:ab,ti OR textile:ab,ti 7. 5 AND 6 Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in MEDLINE (via PubMed interface).
Search date	3 July 2015
In/Exclusion criteria	**Population**: Include: adults or children in Europe **Intervention**: Include: clothing adapted to environments with a high tick prevalence, including clothing impregnated with tick repellent; Exclude: products to impregnate clothing manually; battle dress uniforms **Outcome**: Include: prevention of tick bites from *Ixodes Ricinus*; number of ticks during field conditions **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values.

	Language: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: Only references from the last 15 years were included (because of resistance to insecticides).

Characteristics of included studies

Author, year Country	Study design	Population	Comparison	Remarks
Rossback, 2014, Germany	Experimental: randomized controlled trial	164 male forestry workers	permethrin-treated vs untreated work trousers The initial permethrin content in all types of treated trousers was between 1,250 – 1,500 mg/m² [data about cut protection trousers were not extracted]	Tick infestation (quantity of ticks on the body surface) was assessed by questionnaire on four consecutive workdays during four predefined weeks of a 16 week study period
Stjernberg, 2005, Sweden	Experimental: randomized controlled trial (within subjects design)	10 volunteers exposed by walking in tick endemic areas (healthy adult males and females (non-pregnant), aged 18-65 y	light vs dark clothing (a T-shirt (100% cotton), a fleece jacket (100% polyester), trousers (100% cotton) and soft leather shoes) The 10 participants were randomized into 2 standardized exposure groups. In the first group, 2/5 wore light clothing and 3/5 wore dark clothing, and vice versa in the second group. The exposure squares, sited side by side, measured 25x25 m. The participants were exposed twice in each square; once wearing light clothing and once wearing dark clothing.	Each participant had 2 persons searching and collecting ticks on the clothing and placing them into cryo tubes

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Tick infestation rate	Permethrin-treated vs untreated work trousers	Statistically significant: 36.6% vs 63.4% £† (p=0.001) *In favour of permethrin-treated work trousers*	1, 82 vs 82 §	Rossback, 2014
Average number of ticks per workday		Statistically significant: 0.13 vs 0.44 £† (p<0.001) *In favour of permethrin-treated work trousers*		
Number of ticks during 6 exposures of 3.5 h	Light vs dark clothing	Statistically significant: 54.7±18.1 vs 33.9±9.2 MD: 20.8, 95%CI [8.98; 32.62] (p=0.003)	1, 10 vs 10 (within subjects) §	Stjernberg, 2005

		In favour of dark clothing		

£ No effect size and CI available
† Imprecision (lack of data)
§ Imprecision (limited sample size)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Rossback, 2014	Yes (Subjects were aware of their group affiliation since the permethrin treated trousers were respectively labeled)	Yes	No	No	Since participation in this study was voluntary, a selection bias cannot be excluded. Respondents showing high tick susceptibility or a history of tick-borne diseases might be overrepresented in the presented study population
Stjernberg, 2005	Yes (allocation concealment not possible)	Yes	No	No	Within subjects design

Level of evidence
Impregnated trousers

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/lack of data
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Dark clothing

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion(s)	**Impregnated clothing** There is limited evidence in favour of permethrin impregnated trousers. It was shown that wearing permethrin impregnated trousers resulted in a statistically significant decreased tick infestation rate and average number of ticks per workday, compared to wearing untreated trousers (Rossback 2014). Evidence is of low quality and results cannot be considered precise due to limited sample size and lack of data. **Dark clothing** There is limited evidence in favour of dark clothing. It was shown that wearing dark coloured clothing resulted in a statistically significant decreased number of ticks, compared to wearing light coloured clothing (Stjernberg, 2005). Evidence is of low quality and results cannot be considered precise due to limited sample size.

Reference(s)	**Articles** Roßbach B, Kegel P, Zier U, Niemietz A, Letzel S. *Protective efficacy of permethrin-treated trousers against tick infestation in forestry workers*. Annals of Agricultural and Environmental Medicine 2014, 21:712-717 Stjernberg L, Berglund J. *Detecting ticks on light versus dark clothing.* Scand J Infect Dis 2005, 37(5):361-4

Tick bite – Insect repellent (Prevention)

Question (PICO)	Among adults and children (P), does the use of tick repellent (I) compared to not using this or using another product (C) prevent tick bites (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: ([mh "Ticks"] OR [mh "Tick Control"] OR [mh "Tick Bites"] OR tick*:ti,ab,kw) AND ([mh "Insecticides"] OR (insecticide):ti,ab,kw OR (repellent):ti,ab,kw) **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Ticks"[Mesh] OR tick*[TIAB] OR "Tick Control"[Mesh] OR "Tick Bites"[Mesh] 2. "Insecticides"[Mesh] OR insecticide[TIAB] OR repellent[TIAB] 3. "Primary Prevention"[Mesh:NoExp] OR "Preventive Medicine"[Mesh] OR "Prevention and control "[Subheading] 4. 1-3 AND **Embase** (via Embase.com interface) for experimental and observational studies using the following search strategy: 1. 'tick'/exp OR tick*:ab,ti OR 'tick bite'/exp 2. 'insecticide'/exp OR 'insect control'/exp OR insecticide:ab,ti OR repellent:ab,ti 3. 'prevention'/exp OR 'preventive medicine'/exp OR *'prevention':lnk* 4. 1-3 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in MEDLINE (via PubMed interface).
Search date	3 July 2015
In/Exclusion criteria	**Population**: Include: adults or children in Europe; Exclude: animals **Intervention**: Include: insecticide or natural repellent against ticks that is easily available (pharmacy or supermarket) in Belgium, including products containing para-menthane-diol (PMD), DEET, IR3535, icaridine (picaridine/KBR322/ Bayrepel), ethyl-N-acetyl-N-butyl-beta-alaninaat and natural oils. Studies making a comparison of products were also included. **Outcome**: Include: prevention of tick bites of *Ixodes Ricinus* ticks (because of prevalence in Belgium); number of ticks, protection times, repellent efficacy **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available.

	Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: Only references from the last 15 years were included (because of resistance to insecticides).

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Büchel, 2015, Germany	Experimental: randomized controlled trial (within subjects design)	10 volunteers who received active nymphs (*Ixodes ricinus*, *Ixodes scapularis*) on their forearm [only data for *Ixodes ricinus* were extracted]	Intervention: 1. 10% EBAAP (3-[N-butyl-N-acetyl]-aminopropionic acid, ethyl ester) 2. 10% Icaridin ((2-(2-hydroxyethyl)-1-piperidinecarboxylic acid 1-methylpropyl ester 3. 20% DEET (N,N-diethyl-3-methylbenzamide) Ethanolic solutions of the active ingredients of the repellents were applied at 1.0 µl cm^{-2}. After pretesting with the full standard amount, the dose was reduced in order to yield protection times below10 h. Exposure began 20 min after application of the test formulations.	The upward movement of ticks was monitored until repellent failure taking up to 12.5 h
Staub, 2002, Switzerland	Experimental: randomized controlled trial	276 forestry workers and orienteers under everyday conditions in Switzerland. Subjects over 12 years old who had reported at least 2 tick bites in a questionnaire and who gave written informed consent were included. Individuals with a history of chronic or acute skin disease, with open or nonhealing wounds, or with an inclination to use other commercially available repellents during the study period were excluded.	Insect repellent spray (Parapic-Tick-Repellent, BIOMED AG, Dübendorf, Switzerland) containing both 15.0% DEET and 15.0% EBAAP vs placebo (isopropanol and propylene glycol) Participants were instructed to apply the preparation to uncovered skin and to the adjacent 10 cm of skin covered by clothing (excluding the face) just before spending time in the forest, and a second application 4 hours after the first.	In a log, information of 10 days was requested: date, the geographical location, and the amount of time in the forest. The numbers of attached ticks (skin) and unattached ticks (skin or clothing), as well as the location of attached ticks, were recorded.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Protection times	1. EBAAP 2. DEET 3. Icaridin	Not statistically significant: 1 vs 2: 4 h vs 4 h £† <u>Statistically significant</u>: 1 vs 3: Data from graph: 4 h vs 5 h £† (p<0.001) *In favour of icaridin vs EBAAP* <u>Statistically significant</u>: 2 vs 3: Data from graph: 4 h vs 5 h £† (p<0.01) *In favour of icaridin vs DEET*	1, 10 vs 10 § (within subjects)	Büchel, 2015
Percentage of ticks walking onto treated skin (Mean ± SE)		<u>Statistically significant</u>: 1 vs 3: 71±5 vs 60±4 £† (p<0.001) *In favour of icaridin vs EBAAP*		
Percentage of non-repelled ticks (Mean ± SE)		<u>Statistically significant</u>: 1 vs 3: 12±3 vs 3±1 £† (p<0.01) *In favour of icaridin vs EBAAP* <u>Statistically significant</u>: 2 vs 3: 12±3 vs 3±1 £† p<0.001 *In favour of icaridin vs DEET*		
Number of tick bites per hour (Mean ± SEM)	EBAAP + DEET vs placebo	<u>Statistically significant</u>: 0.10±0.016 vs 0.17±0.029 £† (p<0.05) *In favour of EBAAP+DEET*	1, 138 vs 138 §	Staub, 2002
Repellent efficacy		<u>Statistically significant</u>: No raw data available 41.1%, 95%CI [2.5;79.6] (p<0.05) *In favour of EBAAP+DEET*		

£ No effect size and CI available
† Imprecision (lack of data)
§ Imprecision (limited sample size)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Büchel, 2015	Unclear (random assignment of treatments, but unclear how this was done)	Unclear (no information provided)	No	No	Ethanol was applied as it is a good solvent for all active ingredients tested. Although it is a commonly used solvent it might have an influence on the repellent properties. It can be speculated, that a repellent product might be less efficient at field conditions than the results gained in the present study.

Staub, 2002	Unclear (random assignment of treatments, but unclear how this was done)	No (double blind)	No	No	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/lack of data
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Moderate [B]**	

Conclusion(s)	There is limited evidence in favour of using insect repellents against ticks. It was shown that icaridin resulted in a statistically significant increased protection time and decrease in the percentage of ticks walking onto treated skin and percentage of non-repelled ticks compared to EBAAP (Büchel 2015). In addition it was shown that icaridin resulted in a statistically significant increased protection time and decrease in the percentage of non-repelled ticks compared to EBAAP (Büchel 2015). In another study it was shown that EBAAP + DEET resulted in a statistically significant decreased number of tick bites per hour (Staub 2002) compared to placebo. Evidence is of moderate quality and results cannot be considered precise due to limited sample size and lack of data.
Reference(s)	**Articles** Staub D, Debrunner M, Amsler L, Steffen R. *Effectiveness of a repellent containing DEET and EBAAP for preventing tick bites.* Wilderness Environ Med 2002, 13(1):12-20 Büchel K, Bendin J, Gharbi A, Rahlenbeck S, Dautel H. *Repellent efficacy of DEET, Icaridin, and EBAAP against Ixodes ricinus and Ixodes scapularis nymphs (Acari, Ixodidae)*. Ticks and Tick-borne Diseases 2015, 6:4(494-498)

Tick bites – Aloe Vera (Prevention)

Question (PICO)	In healthy people (P), does prophylaxis with Aloe Vera (I), compared to not treating with Aloe Vera (C), influence the prevalence of tick bites (O)?
Search Strategy	Databases: **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "ticks"] OR [mh "tick bites"] OR (tick*):ti,ab,kw OR (ixodida*):ti,ab,kw 2. [mh "aloe"] OR (aloe*):ti,ab,kw OR (aloe vera*):ti,ab,kw 3. #1 AND #2 **MEDLINE** (via PubMed interface) for systematic reviews, experimental and observational studies using the following search strategy: 1. "ticks"[MeSH] OR "tick bites"[MeSH] OR "tick*"[TIAB] OR "ixodida*"[TIAB] 2. "Aloe"[MeSH] OR "Aloe*"[TIAB] OR "Aloe Vera*"[TIAB] 3. #1 AND #2 **Embase** (via Embase.com interface) using the following search strategy: 1. 'tick'/exp OR 'tick bite'/exp OR tick*:ab,ti OR ixodida*:ab,ti 2. 'Aloe'/exp OR Aloe*:ab,ti OR (Aloe NEXT/1 Vera*):ab,ti

	3. #1 AND #2
Search date	20 January 2016
In/Exclusion criteria	**Population:** Include: Healthy people. **Intervention:** Include: prophylaxis with Aloe Vera. Exclude: Any other prophylaxis method. **Comparison:** Include: No prophylaxis, another method of prophylaxis **Outcome:** Include: Prevalence of tick bites **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: observational studies if intervention is already included in experimental studies, case series, cross-sectional studies, animal studies, ex vivo or in vitro studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year:** Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion(s)	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Tick bite – Risk factors

Question (PICO)	In humans (P) which risk factors (RF) exist resulting in tick bites (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "Ticks"] **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Ticks"[Mesh] OR tick*[TIAB] 2. "Bites and Stings"[Mesh] OR bite*[TIAB] 3. 1 AND 2 4. "Tick Bites"[Mesh] 5. 3 OR 4 6. "Risk Factors"[Mesh] OR risk factor*[TIAB] 7. 5 AND 6 **Embase** (via Embase.com interface) using the following search strategy: 1. 'tick'/exp OR tick*:ab,ti 2. 'bites and stings'/exp OR bite*:ab,ti

	3. 1 AND 2 4. 'tick bite'/exp 5. 3 OR 4 6. 'risk factor'/exp OR (Risk NEXT/1 factor*):ab,ti 7. 5 AND 6
Search date	7 July 2015
In/Exclusion criteria	**Population**: Include: adults and children **Intervention**: Include: modifiable, proximal risk factor with a potential immediate implication for practice that results in primary prevention at the household or community level. Risk factors related to healthy persons. Exclude: risk factors that lead to interventions with already proven effectiveness. The risk factor that does not precede the outcome. The risk factor is common sense. **Outcome**: Include: tick bites **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, cross sectional study, and the data are available. Exclude: case series, animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion(s)	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Scabies – Personal hygiene (First aid)

Question (PICO)	In humans with scabies (P) is personal hygiene (I) compared to no personal hygiene (C) effective as a first aid treatment to increase survival, tissue healing, functional recovery, pain, complications, time to resumption of usual activities, restoration to the pre-exposure condition, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "Scabies"] **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Scabies"[Mesh] OR scabies[TIAB] OR "Sarcoptus scabei"[TIAB] 2. "Hand Disinfection"[Mesh] OR hand [TIAB] 3. 1 AND 2

	Embase (via Embase.com interface) using the following search strategy: 1. 'scabies'/exp OR scabies:ab,ti OR 'Sarcoptus scabei':ab,ti 2. *'hand washing'/exp OR hand:ab,ti* 3. *1 AND 2* Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in MEDLINE (via PubMed interface).
Search date	22 June 2015
In/Exclusion criteria	**Population**: Include: people or healthy volunteers with scabies. **Intervention**: Include: personal hygiene, including hand washing or using alcohol-based hand rubs **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
FitzGerald, 2014, Ireland	Systematic review of experimental studies: randomized controlled trials	Index cases with scabies infestation	Prophylactic interventions for contacts of people with scabies to prevent infestation in the contacts (medical treatment and non-medical interventions, such as (1) barrier precautions (including patient isolation, patient cohorting etc), (2) personal hygiene (including hand washing) measures, and (3) environmental decontamination (including advice to wash clothing and bedding))	Selection criteria for study design: RCTs and cluster RCTs Studies that were excluded because of study design were checked for the described intervention
Cinotti, 2015, France	Experimental: non-randomized controlled trial (within subjects design)	A 91-year-old patient with hyperkeratotic scabies, which had been diagnosed by clinical examination and reflectance	(1) hand washing (2) application of 3 different topical antiseptics (two alcohol-based and one povidone–iodine-based); control area without antiseptic application The soap and antiseptics are composed of:	A skin scraping of each area was taken to evaluate the viability of the mites (*Sarcoptes scabiei*) over time with optical microscopy

		confocal microscopy	-soap: Phagoderm, Phagogène, Nantes, France, composed of water, potassium cocoate, glycerine and coconut oil -alcohol gel: Aniosgel 85 NPC, Anios, Lille-Hellemmes, France, containing 755 mL/L ethanol -chlorexidine scrub: Gilbert scrub, Gilbert, Hérouville Saint-Clair, France, containing 5% ethanol and 4% chlorexidine Digluconate -iodine scrub: Betadine, Meda, Paris, France, containing 4% povidone–iodine. The first antiseptic is a 'leave-on' product while the two other antiseptics need to be rinsed off after an appropriate length of time.	

Synthesis of findings

No studies were included in the systematic review (Fitzgerald 2014), or could be included after additional examination of the non-randomized studies.

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Survival of *Sarcoptes scabiei* (number of mites)	Hand washing vs not	Not statistically significant: £† 177 vs 176	1, 1 vs 1 (within subjects) §	Cinotti, 2015
	Alcohol vs not	Not statistically significant: £† 0 h: 47 vs 41 3 h: 48 vs 45 17 h: 51 vs 38 44 h: 54 vs 17		
	Chlorhexidine vs not	Not statistically significant: £† 0 h: 46 vs 41 3 h: 46 vs 45 17 h: 46 vs 38 44 h: 55 vs 17		
	Povidone-iodine vs not	Not statistically significant: £† 0 h: 45 vs 41 3 h: 47 vs 45 17 h: 44 vs 38 44 h: 56 vs 17		

£ No raw SD's available, effect size and CI cannot be calculated

† Imprecision (lack of data)

§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Cinotti, 2015	Unclear; no randomization (within subjects design)	unclear	no	no	within subjects design

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/lack of data
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion(s)	There is limited evidence neither in favour of the intervention nor the control: a statistically significant decrease of the number of mites in case of hand washing or using alcohol-based hand rubs compared to not doing this could not be demonstrated (Cinotti 2015). Evidence is of low quality and results of this study are imprecise due to limited sample size and lack of data.
Reference(s)	**Articles** Cinotti E, Perrot JL, Labeille B, Maguet H, Couzan C, Flori P, Cambazard F. *Inefficacy of alcohol-based hand rub on mites in a patient with hyperkeratotic scabies*. Clin Exp Dermatol 2015, 40(2):177-81 **Systematic reviews** FitzGerald D, Grainger RJ, Reid A. *Interventions for preventing the spread of infestation in close contacts of people with scabies.* Cochrane Database of Systematic Reviews 2014, Issue 2. Art. No.: CD009943.

Scabies – Environmental hygienic measures (Prevention)

Question (PICO)	In humans with scabies (P) is taking environmental hygienic measures (I) compared to not doing this (C) effective to prevent recontamination (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "Scabies"] **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Scabies"[Mesh] OR scabies[TIAB] OR "Sarcoptus scabei"[TIAB] 2. "Bedding and Linens"[Mesh] OR "Clothing"[Mesh] OR "Hygiene"[Mesh] OR bedding[TIAB] OR linen*[TIAB] OR cloth*[TIAB] OR wash*[TIAB] OR "prevention and control"[Subheading] OR prevention[TIAB] 3. 1 AND 2 **Embase** (via Embase.com interface) using the following search strategy: 1. 'scabies'/exp OR scabies:ab,ti OR 'Sarcoptus scabei':ab,ti 2. 'bed'/exp OR 'clothing'/exp OR 'hygiene'/exp OR bedding:ab,ti OR linen*:ab,ti OR cloth*:ab,ti OR wash*:ab,ti OR *'prevention':lnk OR prevention:ab,ti* *3. 1 AND 2*
Search date	22 June 2015
In/Exclusion criteria	**Population**: Include: people or healthy volunteers with scabies **Intervention**: Include: hygienic measures including washing bedding, linens and clothing, and items that were in contact with the mites **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers.

	Design: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
FitzGerald, 2014, Ireland	Systematic review of experimental studies: randomized controlled trials	Index cases with scabies infestation	Prophylactic interventions for contacts of people with scabies to prevent infestation in the contacts (medical treatment and non-medical interventions, such as (1) barrier precautions (including patient isolation, patient cohorting etc), (2) personal hygiene (including hand washing) measures, and (3) environmental decontamination (including advice to wash clothing and bedding))	Selection criteria for study design: RCTs and cluster RCTs Studies that were excluded because of study design were checked for the described intervention

Synthesis of findings

No studies were included in the systematic review, or could be included after additional examination of the non-randomized studies.

Quality of evidence

Not applicable

Conclusion(s)	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	**Systematic review** FitzGerald D, Grainger RJ, Reid A. *Interventions for preventing the spread of infestation in close contacts of people with scabies*. Cochrane Database of Systematic Reviews 2014, Issue 2. Art. No.: CD009943. DOI: 10.1002/14651858.CD009943.pub2.

Lice bite – Pediculicide (First aid)

Question (PICO)	In humans with lice bites (P), does a pediculicide (I) compared to a placebo/alternative method (C) increase time to restoration to the pre-exposure condition and resolution of symptoms (O)?
Search strategy	Databases **NGC** (National Guideline Clearinghouse) using the following search strategy: 'head lice'

	The Cochrane Library (systematic reviews and controlled trials) using the following search strategy: [mh "Lice infestations"] OR [mh "Pediculus"] OR lice:ti,ab,kw OR louse:ti,ab,kw Guidelines, systematic reviews, retrieved with the above searches, and used as source for individual studies: - NGC Guideline: Bohl 2013 - Guidelines for the diagnosis and treatment of pediculosis capitis (head lice) in children and adults 2013. - Cochrane review: Van der Wouden 2015 - Interventions for treating head lice
Search date	22 July 2015
In/Exclusion criteria	**Population**: Include: children or adults with head lice. Exclude: persons with pubic lice or body lice. **Intervention**: Include: interventions with products/methods available in Belgium (such as dimeticon, malathion, permethrine, depallethrine, bioallethrine, piperonylbutoxide) Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences or interventions with products that are forbidden in Belgium as pediculicide (Clofenotan (DDT) and lindane). **Outcome**: Include: restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies. **Language**: Include: English **Publication year:** Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion(s)	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Lice bite – Wet comb method (First aid)

Question (PICO)	In humans with lice bites (P), does the wet comb method (I) compared to doing nothing/an alternative method (C) increase time to restoration to the pre-exposure condition and resolution of symptoms (O)?
Search strategy	Databases **NGC** (National Guideline Clearinghouse) using the following search strategy: 'head lice' **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "Lice infestations"] OR [mh "Pediculus"] OR lice:ti,ab,kw OR louse:ti,ab,kw

	Guidelines, systematic reviews, retrieved with the above searches, and used as source for individual studies: -NGC Guideline: Bohl 2013 - Guidelines for the diagnosis and treatment of pediculosis capitis (head lice) in children and adults 2013. -Cochrane review: Van der Wouden 2015 - Interventions for treating head lice Review wordt later dit jaar nog gepubliceerd !
Search date	22 July 2015
In/Exclusion criteria	**Population**: Include: children or adults with head lice. Exclude: persons with pubic lice or body lice. **Intervention**: Include: interventions with products/methods available in Belgium. Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. **Outcome**: Include: restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies. **Language**: Include: English **Publication year:** Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion(s)	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Lice – Environmental decontamination (First aid)

Question (PICO)	In households with lice (P), does a certain washing/cleaning method (I) compared to an alternative method (C) decrease the risk on reinfestation of lice (O)?
Search strategy	Databases **NGC** (National Guideline Clearinghouse) using the following search strategy: 'head lice' **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "Lice infestations"] OR [mh "Pediculus"] OR lice:ti,ab,kw OR louse:ti,ab,kw Guidelines, systematic reviews, retrieved with the above searches, and used as source for individual studies: -NGC Guideline: Bohl 2013 - Guidelines for the diagnosis and treatment of pediculosis capitis (head lice) in children and adults 2013.

	-Cochrane review: Van der Wouden 2015 - Interventions for treating head lice Review wordt later dit jaar nog gepubliceerd !
Search date	22 July 2015
In/Exclusion criteria	**Population**: Include: households with head lice. Exclude: households with pubic lice or body lice. **Intervention**: Include: interventions with products/methods available in Belgium. Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. **Outcome**: Include: restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies. **Language**: Include: English **Publication year:** Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion(s)	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Bedbug bite – Cooling with ice or cold water (First aid)

Question (PICO)	In humans with a bite of a bedbug (P) is cooling of the bite (I) compared to not cooling (C) effective and feasible for laypersons as a first aid treatment to increase survival, tissue healing, functional recovery, pain, complications, time to resumption of usual activities, restoration to the pre-exposure condition, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "Bedbugs"] **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Bedbugs"[Mesh] OR bedbug*[TIAB] OR Cimex[TIAB] 2. Ice[Mesh] OR cryotherapy[Mesh:NoExp] OR "Cold Temperature"[Mesh] OR Ice[TIAB] OR cryotherapy[TIAB] OR cold therapy[TIAB] OR cold[TIAB] 3. Rins*[TIAB] OR shower [TIAB] OR wash*[TIAB] 4. 2 OR 3 5. 1 AND 4 **Embase** (via Embase.com interface) using the following search strategy: 1. 'Cimex'/exp OR bedbug*:ab,ti OR cimex:ab,ti

	2. 'ice'/exp OR 'cryotherapy'/exp OR ice:ab,ti OR cryotherapy:ab,ti OR cold:ab,ti OR 'cold'/exp 3. Rins*:ab,ti OR shower:ab,ti OR wash*:ab,ti 4. 2 OR 3 5. 1 AND 4
Search date	22 June 2015
In/Exclusion criteria	**Population**: Include: people or healthy volunteers with bedbug bites **Intervention**: Include: cooling, use of ice or ice pack, ice water **Control**: not cooling or another treatment to reduce pain **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion(s)	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Bedbug bite – Washing with water (First aid)

Question (PICO)	In humans with a bite of a bedbug (P) is washing the bite (I) compared to not doing this (C) effective and feasible for laypersons as a first aid treatment to increase survival, tissue healing, functional recovery, pain, complications, time to resumption of usual activities, restoration to the pre-exposure condition, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "Bedbugs"] **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Bedbugs"[Mesh] OR bedbug*[TIAB] OR Cimex[TIAB]

	2. Ice[Mesh] OR cryotherapy[Mesh:NoExp] OR "Cold Temperature"[Mesh] OR Ice[TIAB] OR cryotherapy[TIAB] OR cold therapy[TIAB] OR cold[TIAB] 3. Rins*[TIAB] OR shower [TIAB] OR wash*[TIAB] 4. 2 OR 3 5. 1 AND 4 **Embase** (via Embase.com interface) using the following search strategy: 1. 'Cimex'/exp OR bedbug*:ab,ti OR cimex:ab,ti 2. 'ice'/exp OR 'cryotherapy'/exp OR ice:ab,ti OR cryotherapy:ab,ti OR cold:ab,ti OR 'cold'/exp 3. Rins*:ab,ti OR shower:ab,ti OR wash*:ab,ti 4. 2 OR 3 5. 1 AND 4
Search date	22 June 2015
In/Exclusion criteria	**Population**: Include: people or healthy volunteers with bedbug bites **Intervention**: Include: washing, rinsing, irrigating with water **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion(s)	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Oak processionary caterpillar irritation – Showering (First aid)

Question (PICO)	In humans with irritation due to the oak processionary caterpillar (P), is showering (I) compared to not showering (C) effective and feasible for laypersons as a first aid treatment to increase survival, tissue healing, functional recovery, pain, complications, time to resumption of usual activities, restoration to the pre-exposure condition, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "Lepidoptera"] OR caterpillars:ti,ab,kw OR lepidopterism:ti,ab,kw OR Thaumotopoea:ti,ab,kw OR 'Oak processionary':ti,ab,kw OR 'caterpillar dermatitis':ti,ab,kw OR lepidoptera:ti,ab,kw **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Lepidoptera"[Mesh] OR caterpillars [TIAB] OR lepidopterism [TIAB] OR Thaumotopoea [TIAB] OR "Oak processionary"[TIAB] OR "caterpillar dermatitis" [TIAB] OR "lepidoptera" [TIAB] 2. "Bites and Stings"[Mesh] 3. 1 AND 2 4. "First Aid"[Mesh] OR "Emergency Treatment"[Mesh:NoExp] OR "Primary Health Care"[Mesh:NoExp] OR "Acute disease"[Mesh] OR "emergencies" [Mesh] OR "self care"[Mesh] OR "acute management" [TIAB] OR "immediate care" [TIAB] OR "prehospital treatment" [TIAB] 5. 1 AND 4 6. Rins*[TIAB] OR shower [TIAB] OR wash*[TIAB] OR hot[TIAB] OR "Hot Temperature"[Mesh] OR "Ointments"[Mesh] OR "Emollients"[Mesh] OR cream [TIAB] OR ointment*[TIAB] OR lotion*[TIAB] 7. 1 AND 6 8. 3 OR 5 OR 7 **Embase** (via Embase.com interface) using the following search strategy: 1. 'Lepidoptera'/exp OR caterpillars:ab,ti OR lepidopterism:ab,ti OR Thaumotopoea:ab,ti OR 'Oak processionary':ab,ti OR 'caterpillar dermatitis':ab,ti OR lepidoptera:ab,ti 2. 'bites and stings'/exp 3. 1 AND 2 4. 'first aid'/exp OR 'emergency treatment'/exp OR 'primary health care'/exp OR 'emergency'/exp OR 'self care'/exp Or 'acute management':ab,ti OR 'immediate care':ab,ti OR 'prehospital treatment':ab,ti 5. 1 AND 4 6. Rins*:ab,ti OR shower:ab,ti OR wash*:ab,ti OR hot:ab,ti OR 'heat'/exp OR 'ointment'/exp OR 'emollient agent'/exp OR cream:ab,ti OR ointment*:ab,ti OR lotion*:ab,ti 7. 1 AND 6 8. 3 OR 5 OR 7
Search date	22 June 2015
In/Exclusion criteria	**Population**: Include: people or healthy volunteers with irritation due to the oak processionary caterpillar **Intervention**: Include: showering, washing away, irrigation with water **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers.

	Design: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion(s)	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Oak processionary caterpillar irritation – Hot washing of clothing (First aid)

Question (PICO)	In humans with irritation due to the oak processionary caterpillar (P), is hot washing of clothing (I) compared to not doing this (C) effective and feasible for laypersons as a first aid treatment to increase survival, tissue healing, functional recovery, pain, complications, time to resumption of usual activities, restoration to the pre-exposure condition, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "Lepidoptera"] OR caterpillars:ti,ab,kw OR lepidopterism:ti,ab,kw OR Thaumotopoea:ti,ab,kw OR 'Oak processionary':ti,ab,kw OR 'caterpillar dermatitis':ti,ab,kw OR lepidoptera:ti,ab,kw **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Lepidoptera"[Mesh] OR caterpillars [TIAB] OR lepidopterism [TIAB] OR Thaumotopoea [TIAB] OR "Oak processionary"[TIAB] OR "caterpillar dermatitis" [TIAB] OR "lepidoptera" [TIAB] 2. "Bites and Stings"[Mesh] 3. 1 AND 2 4. "First Aid"[Mesh] OR "Emergency Treatment"[Mesh:NoExp] OR "Primary Health Care"[Mesh:NoExp] OR "Acute disease"[Mesh] OR "emergencies" [Mesh] OR "self care"[Mesh] OR "acute management" [TIAB] OR "immediate care" [TIAB] OR "prehospital treatment" [TIAB] 5. 1 AND 4

	6. Rins*[TIAB] OR shower [TIAB] OR wash*[TIAB] OR hot[TIAB] OR "Hot Temperature"[Mesh] OR "Ointments"[Mesh] OR "Emollients"[Mesh] OR cream [TIAB] OR ointment*[TIAB] OR lotion*[TIAB] 7. 1 AND 6 8. 3 OR 5 OR 7 **Embase** (via Embase.com interface) using the following search strategy: 1. 'Lepidoptera'/exp OR caterpillars:ab,ti OR lepidopterism:ab,ti OR Thaumotopoea:ab,ti OR 'Oak processionary':ab,ti OR 'caterpillar dermatitis':ab,ti OR lepidoptera:ab,ti 2. 'bites and stings'/exp 3. 1 AND 2 4. 'first aid'/exp OR 'emergency treatment'/exp OR 'primary health care'/exp OR 'emergency'/exp OR 'self care'/exp Or 'acute management':ab,ti OR 'immediate care':ab,ti OR 'prehospital treatment':ab,ti 5. 1 AND 4 6. Rins*:ab,ti OR shower:ab,ti OR wash*:ab,ti OR hot:ab,ti OR 'heat'/exp OR 'ointment'/exp OR 'emollient agent'/exp OR cream:ab,ti OR ointment*:ab,ti OR lotion*:ab,ti 7. 1 AND 6 8. 3 OR 5 OR 7
Search date	22 June 2015
In/Exclusion criteria	**Population**: Include: people or healthy volunteers with irritation due to the oak processionary caterpillar **Intervention**: Include: washing of clothing at hot temperature **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion(s)	No relevant studies were identified the above search strategy and criteria.
Reference(s)	/

Scorpion sting and spider bite – Limb elevation (First aid)

Question (PICO)	In humans with a scorpion sting or spider bite (P) is limb elevation (I) compared to no elevation (C) effective and feasible for laypersons as a first aid treatment to increase survival, tissue healing, functional recovery, pain, complications, time to resumption of usual activities, restoration to the pre-exposure condition, time to resolution of symptoms? (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "Scorpion Stings"] OR [mh "Scorpions"] OR [mh "Spider bites"] **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Scorpion Stings"[Mesh] OR "Spider Bites"[Mesh] OR (("Scorpions"[Mesh] OR "Spiders"[Mesh]) AND "Bites and Stings"[Mesh]) OR ((scorpion*[TIAB] OR spider*[TIAB]) AND (bite*[TIAB] OR sting*[TIAB])) 2. "Posture"[Mesh] OR Elev*[TIAB] OR Ice[Mesh] OR cryotherapy[Mesh:NoExp] OR "Cold Temperature"[Mesh] OR Ice[TIAB] OR cryotherapy[TIAB] OR cold therapy[TIAB] OR cold[TIAB] 3. 1 AND 2 **Embase** (via Embase.com interface) using the following search strategy: 1. 'scorpion sting'/exp OR 'spider bite'/exp OR ('bites and stings'/exp AND ('spider'/exp OR 'scorpion'/exp)) OR ((scorpion*:ab,ti OR spider*ab,ti) AND (bite*:ab,ti OR sting*ab,ti)) 2. elev*:ab,ti OR 'body posture'/exp OR 'ice'/exp OR 'cryotherapy'/exp OR ice:ab,ti OR cryotherapy:ab,ti OR cold:ab,ti OR 'cold'/exp 3. 1 AND 2
Search date	22 June 2015
In/Exclusion criteria	**Population**: Include: people with a scorpion sting or spider bite **Intervention**: Include: elevation of bitten limb **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion(s)	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Scorpion sting and spider bite – Cooling with ice or cold water (First aid)

Question (PICO)	In humans with a scorpion sting or spider bite (P) is cooling of the bite (I) compared to not cooling (C) effective and feasible for laypersons as a first aid treatment to increase survival, tissue healing, functional recovery, pain, complications, time to resumption of usual activities, restoration to the pre-exposure condition, time to resolution of symptoms? (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "Scorpion Stings"] OR [mh "Scorpions"] OR [mh "Spider bites"] **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Scorpion Stings"[Mesh] OR "Spider Bites"[Mesh] OR (("Scorpions"[Mesh] OR "Spiders"[Mesh]) AND "Bites and Stings"[Mesh]) OR ((scorpion*[TIAB] OR spider*[TIAB]) AND (bite*[TIAB] OR sting*[TIAB])) 2. "Posture"[Mesh] OR Elev*[TIAB] OR Ice[Mesh] OR cryotherapy[Mesh:NoExp] OR "Cold Temperature"[Mesh] OR Ice[TIAB] OR cryotherapy[TIAB] OR cold therapy[TIAB] OR cold[TIAB] 3. 1 AND 2 **Embase** (via Embase.com interface) using the following search strategy: 1. 'scorpion sting'/exp OR 'spider bite'/exp OR ('bites and stings'/exp AND ('spider'/exp OR 'scorpion'/exp)) OR ((scorpion*:ab,ti OR spider*ab,ti) AND (bite*:ab,ti OR sting*ab,ti)) 2. elev*:ab,ti OR 'body posture'/exp OR 'ice'/exp OR 'cryotherapy'/exp OR ice:ab,ti OR cryotherapy:ab,ti OR cold:ab,ti OR 'cold'/exp 3. 1 AND 2 Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in MEDLINE (via PubMed interface)
Search date	22 June 2015
In/Exclusion criteria	**Population**: Include: people or healthy volunteers with a scorpion sting or spider bite **Intervention**: Include: cooling, use of ice or ice pack **Control**: not cooling or another treatment to reduce pain **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available.

	Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Aksel, 2015, Turkey	Experimental: Randomized controlled trial	130 patients (age over 18) with painful scorpion stings who did not have any systemic signs or symptoms, presenting to the ED. Patients were randomly allocated to paracetamol group (n=45, 34.6%), topical lidocaine group (n=43, 33.1%), and ice application group (n=42, 32.3%).	Patients were treated with intravenous paracetamol (1 gram of intravenous paracetamol), topical lidocaine, or ice application (ice packs were applied to the sting site intermittently for 10 min and was performed 3 times with 10-min intervals). [only data on ice application and paracetamol were extracted]	Pain intensity was evaluated using visual analog scale (VAS) score (0 to 100 mm; 0 = no pain, 100 = worst possible pain)

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Change in pain intensity VAS score from baseline (mm)	Ice application vs paracetamol	Not statistically significant: £† After 30 min: 14.50 (0-40) vs 10.00 (0-40) (p=0.624) After 60 min: 23.00 (0-50) vs 20.00 (0-60) (p=0.505) After 120 min: 30.00 (0-70) vs 35.00 (0-90) (p=0.348) After 240 min: 45 (33.75-55.25) vs 45 (28-62.5) (p=1.000)	1, 42 vs 45 §	Aksel, 2015

Values are expressed as Medians (minimum-maximum)
£ No effect size and CI available
§ Imprecision (limited sample size)
† Imprecision (lack of data)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Aksel, 2015	No	No	No	No	Absence of a placebo group

Level of the body of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	
Imprecision	-1	limited sample size
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Moderate [B]**	

Conclusion(s)	There is limited evidence neither in favour of the intervention nor the control: a statistically significant difference of pain intensity using ice compared to paracetamol could not be demonstrated (Aksel 2015). Evidence is of moderate quality and results of this study are imprecise due to limited sample size.
Reference(s)	**Articles** Aksel G, Güler S, Doıan NÖ, Çorbacioılu ŞK. *A randomized trial comparing intravenous paracetamol, topical lidocaine, and ice application for treatment of pain associated with scorpion stings*. Hum Exp Toxicol 2015, 34(6):662-667

Snakebite – Pressure immobilisation (First Aid)

Question (PICO)	In humans with a snakebite (P) is pressure immobilisation (I) compared to no pressure immobilisation (C) effective and feasible for laypersons as a first aid treatment to increase survival, tissue healing, functional recovery, pain, complications, time to resumption of usual activities, restoration to the pre-exposure condition, time to resolution of symptoms? (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "snake bites"] OR [mh "snake venoms"] OR snakebite*:ti,ab,kw OR 'snake bite':ti,ab,kw OR 'snake bites':ti,ab,kw OR 'snake envenomation':ti,ab,kw **MEDLINE** (via PubMed interface) for guidelines and systematic reviews using the following search strategy: 1. Snakebite[Mesh] OR "snake venoms"[Mesh] OR snakebite*[TIAB] OR "snake bite*"[TIAB] OR "snake envenomation*"[TIAB] 2. Bandage[Mesh] OR bandage*[TIAB] OR pressure[Mesh] OR pressure*[TIAB] OR immobilization[Mesh] OR immobili*[TIAB] OR tourniquet[Mesh] OR tourniquet*[TIAB] OR suction[Mesh] OR irrigation[Mesh] OR extract*[TIAB] OR suction*[TIAB] OR suck*[TIAB] OR aspirat*[TIAB] OR irrigat*[TIAB] OR ice[TIAB] OR cryotherapy[Mesh] OR cryotherapy[TIAB] OR cold[TIAB] 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Snakebite/exp 'snake venom'/exp OR snakebite*:ab,ti OR 'snake bite':ab,ti OR 'snake bites':ab,ti OR 'snake envenomation':ab,ti 2. 'Bandages and dressing'/exp OR bandage:ab,ti OR pressure/exp OR pressure*:ab,ti OR immobilization/exp OR immobili*:ab,ti OR tourniquet/de OR tourniquet*:ab,ti OR suction/exp OR 'wound irrigation'/exp OR extract*:ab,ti OR suction*:ab,ti OR suck*:ab,ti OR aspirat*:ab,ti OR irrigat*:ab,ti OR ice:ab,ti OR cryotherapy/exp OR cryotherapy:ab,ti OR cold:ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in MEDLINE (via PubMed interface).
Search date	20 March 2015
In/Exclusion criteria	**Population**: Include: People with a snakebite. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence).

	Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Anker, 1982, Australia	Experimental: Non-randomized controlled trial	12 healthy volunteers, aged 19-31 years were subcutaneously injected with mock venom (radioactive sodium iodide). 3 treatment methods (n=3 in each group)were compared with an untreated group (n=3)	1. CSL method: Elastic or crepe roller bandages (pressure 7.3±0.7 kPa) + padded straight wooden splint to medial side of lower limb 2. Pneumatic splint: full-length lower limb airsplint, pressure maintained at 7.3 kPa 3. Monash method: firm cloth pad over injection site. Pad was held in place by 2 broad bandages firmly binding it to the leg 4. No treatment [Data of pneumatic splint were not extracted]	
Anker, 1983, Australia	Experimental: Non-randomized controlled trial	12 healthy volunteers, aged 18-28 years were subcutaneously injected with mock venom (radio-ionidated insulin). 3 treatment methods (n=3 in each group)were compared with an untreated group (n=3)	1. CSL method: Elastic or crepe roller bandages (pressure 7.3±0.7 kPa) + padded straight wooden splint to medial side of lower limb 2. Pneumatic splint: full-length lower limb airsplint, pressure maintained at 7.3 kPa 3. Monash method: firm cloth pad over injection site. Pad was held in place by 2 broad bandages firmly binding it to the leg 4. No treatment	

			[Data of pneumatic splint were not extracted]	
Howarth, 1994, USA	Experimental: non-randomized controlled trial (within subject design with comparison groups)	15 healthy volunteers (6 women, 9 men) aged 24-47 years, received a subcutaneous injection in wrists/ankles with mock venom (^{99m}Technetium antimony sulphur colloid) in supine position. Venom spread was measured for 2 comparisons	1. Crepe bandage and splint (one lower and one upper limb) vs no treatment (limb without bandage) 2. Crepe bandage and splint (one lower and one upper limb) in rest vs while walking	
Pe, 1994, Myanmar	Experimental: Non-randomized controlled trial	22 healthy male volunteers, mean age 35 years (range 22-58 years), were subcutaneously injected with mock venom. 14 subjects were pad-treated, 8 subjects were untreated controls Mock venom: radioactive iodine NaI^{131}	1. Pad-treated group: a firm rubber pad and cotton bandage was applied immediately over site of injection. Limb was immobilized with bamboo splints 2. Untreated control group Duration of treatment: 45-79 min	
FEASIBILITY				
Canale, 2009, Australia	Experimental: Randomized controlled trial	96 subjects were asked to apply a pressure bandage to a human lower limb in a simulated setting of a snakebite.	Training vs no training in applying an elasticized bandage	
Norris, 2005, USA	Experimental: non-randomized trial	40 volunteers (20 lay subjects and 20 emergency medicine physicians) each performed pressure immobilization 5 times (own nondominant arm, own dominant arm, own dominant leg, arm investigator, leg investigator). Pressure was measured by skin interface pressure (SIP) measurement device placed at simulated snake bite. Lay volunteer applications (n=100) were compared with medical volunteer applications (n=100)	Bandage application by laypersons vs bandage application by emergency medicine physician	
Simpson, 2008, India	Experimental: Randomized controlled trial	40 volunteers (32 males, 8 females, age range 21-72 years) were randomised into 2 groups. Group 1 (n=20) received only written instruction, group 2 (n=20) received further specific training	Group 1: only written instructions on application of pressure immobilisation, randomised in subgroups (crepe bandage or turban cloths and upper or lower limb) Group 2: 4h training on application of pressure immobilisation, randomised in	

			subgroups (crepe bandage or turban cloths)	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Time to peak 80% radioactivity in venous blood sample	Elastic bandage + splint vs no treatment	Not statistically significant: 26.0±17.06 vs 26.0±3.61¤ MD: 0.0, 95%CI [-19.73; 19.73] (p=1.00)*¥	1, 3 vs 3 §	Anker, 1982
	Firm pad and non-elastic bandage + splint vs no treatment	Statistically significant: 74.3±3.79 vs 26.0±3.61¤ MD: 47.30, 95%CI [41.38, 53.22], (p<0.00001)* *In favour of firm pad and non-elastic bandage*		
		66.07±9.71 vs 42.38±5.01¤ MD: 23.69, 95%CI [17.53, 29.85] (p<0.00001)* *In favour of firm pad and non-elastic bandage*	1, 14 vs 8 §	Pe, 1994
Level of radioactivity in blood sample (% of max radioactivity in blood by 60 min)	Elastic bandage + splint vs no treatment	Not statistically significant: 40.67±4.51 vs 46.33±16.17¤ MD: -5.66, 95%CI [-24.66; 13.34] (p=0.56)* ¥	1, 3 vs 3 §	Anker, 1983
	Firm pad and non-elastic bandage + splint vs no treatment	Statistically significant: 4.67±3.25 vs 46.33±16.17¤ MD: -41.66, 95%CI [-60.32, -23.00] (p<0.0001)* *In favour of firm pad and non-elastic bandage*		
No transit of mock venom from periphery to systemic circulation with elastic bandage and splints	Rest vs while walking	a) Lower limbs Statistically significant: 9/13 vs 0/9 OR: 40.11, 95%CI [1.89; 852.92] (p=0.02)* ¥ *In favour of rest* b) Upper limbs Not statistically significant: 6/13 vs 0/6 OR: 11.27, 95%CI [0.53; 240.82] (p=0.12)* ¥	1, 13 vs 9 §	Howarth, 1994
	Firm pad and non-elastic bandage + splint vs no treatment	Statistically significant: 12/14 vs 0/8 OR: 85.00, 95%CI [3.61, 2001.33] (p=0.006)* *In favour of firm pad non-elastic bandage*	1, 14 vs 8	Pe, 1994
FEASIBILITY				
Application of elastic bandage with optimal pressure range (59±9 mmHg)	Training vs no training	Statistically significant: 18/36 vs 5/36 OR: 6.20, 95%CI [1.97; 19.55] (p=0.002) ¥ *In favour of training*	1, 36 vs 36 § (within subjects)	Canale, 2009

Entire technique of bandage application correct	Lay volunteers vs medical volunteers	Not statistically significant: 5/100 vs 13/100 OR: 0.35, 95%CI [0.12; 1.03] (p=0.06)*	1, 100 vs 100 §	Norris, 2005
Correct pressure achieved		14/100 vs 17/100 OR: 0.79, 95%CI [0.37; 1.71] (p=0.56)*¥		
Bandage with optimal pressure range (55-70 mmHg), 1h after training	Crepe bandage vs Turban cloth	Not statistically significant: 5/10 vs 7/10 OR: 0.43, 95%CI [0.07; 2.68] (p=0.37)*¥	1, 10 vs 10 §	Simpson, 2008
	Focused training vs written instructions	Statistically significant: 12/20 vs 0/20 OR: 60.29, 95%CI [3.20; 1137.79] (p=0.006)* *In favour of focused training*	1, 20 vs 20 §	
Bandage pressure (mmHg), 1h after training		57.7±17.0 vs 10.5±11.0 MD: 47.20, 95%CI [38.33; 56.07] (p<0.00001)* *In favour of focused training*		
	Crepe bandage vs Turban cloth	Not statistically significant: 57.9±18.8 vs 57.5±16.0 MD: 0.40, 95%CI [-14.90; 15.70] (p=0.96)*	1, 10 vs 10 §	

Mean ± SD (unless otherwise indicated)

* Calculations done by the reviewer(s) using Review Manager software

¤ Mean and SD for each group calculated from subject data in Excel

¥ Imprecision (large variability of results)

§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Anker, 1982	Yes, no randomisation	Yes, but treatment could not be blinded	No	No	Mock venom (indirectness)
Anker, 1983	Yes, no randomization	Yes, but treatment could not be blinded	No	No	Mock venom (indirectness)
Canale, 2009	Yes (within subject design)	Yes, but treatment could not be blinded	No	No	Simulated setting and healthcare workers (indirectness)
Howarth, 1995	Yes (within subject design)	Yes, but no impact	No	No	Mock venom (indirectness)
Norris, 2005	Yes, not randomized	Yes, but no impact	No	No	Simulated setting, absence of stress of a situation with a real snakebite
Pe, 1994	Unclear	Yes, but no impact	No	No	Mock venom (indirectness) Injection dose varies between subjects
Simpson, 2008	Unclear, randomized, but not stated how	Yes, but no impact	No	No	Simulated setting, absence of stress of a situation with a real snakebite

Level of evidence
Effectiveness:

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/lack of data/large variability of the results
Inconsistency	0	
Indirectness	-1	Mock venom
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Feasibility:

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/lack of data/large variability of the results
Inconsistency	0	
Indirectness	-1	Simulated situations
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	**<u>Effectiveness</u>** There is limited evidence from 2 experimental studies, neither in favour of using an elastic bandage + splint nor the control (no first aid treatment). A statistically significant decrease of speed of venom spread, using **elastic bandage + splint** compared to no first aid treatment, could not be demonstrated (Anker 1982 and 1983). Evidence is of low quality and results of these studies are imprecise due to limited sample size and/or large variability of results. There is limited evidence from 4 experimental studies in favour of **firm pad + non-elastic bandage**. It was shown that the use of a firm pad + non-elastic bandage resulted in a statistically significant decrease of speed of venom spread or transit of mock venom, compared to no treatment (Anker 1982 and 1983, Howarth 1994 and Pe 1994). Evidence is of low quality and results cannot be considered precise due to limited sample size and/or large variability of results. There is limited evidence from 1 experimental studies in favour of **rest (with elastic bandage and splint)**. It was shown that rest (with elastic bandage and splint) resulted in a statistically significant decrease of transit of mock venom, compared to no treatment (Howarth 1994). Evidence is of low quality and results cannot be considered precise due to limited sample size and/or large variability of results. **<u>Feasibility</u>** There is limited evidence from 2 experimental studies in favour of **training laypeople in application of an elastic bandage**. It was shown that training resulted in a statistically significant increase of bandage application with optimal pressure range, compared to written instructions (Canale 2009, Simpson 2008). However, it was shown that lay volunteers did not succeed in a statistically significant higher correct bandage application or achievement of correct pressure, compared to medical volunteers (Norris 2005). Evidence is of low quality and results cannot be considered precise due to limited sample size and/or large variability of results.
Reference(s)	**<u>Articles</u>**

	Anker RL, Straffon WG, Loiselle DS, Anker KM. *Retarding the update of "mock venom" in humans. Comparison of three first-aid treatments.* Med J Aust 1982, 1:212-214 Anker RL, Straffon WG, Loiselle DS, Anker KM. *Comparison of three methods designed to delay uptake of "mock venom"*. Australian Family Physician 1983, 12(5):365-367 Canale E, Isbister GK, Currie BJ. *Investigating the pressure bandaging for snakebite in a simulated setting: Bandage type, training and the effect of transport*. Emergency medicine Australasia 2009, 21:184-190 Howarth DM, Southee AE, Whyte IM. *Lymphatic flow rates and first-aid in simulated peripheral snake or spider envenomation*. Med J Aust 1994, 161(11-12):695-700 Norris RL, Ngo J, Nolan K, Hooker G. *Physicians and lay people are unable to apply pressure immobilization properly in a simulated snakebite scenario*. Wilderness Environ Med 2005, 16:16-21 Tun-Pe, Muang-Muang-Thwin, Myint-Myint-Than, Aye-Aye-Myint, Kyaw-Myint, Thein Than. *The efficacy of compression immobilization technique in retarding spread of radio-labeled Russell's viper venom in Rhesus monkeys and 'mock venom' NaI^{131} in human volunteers.* Southeast Asian J Trop Med Public Health 1994, 25(2):349-353 Simpson ID, Tanwar PD, Andrade C, Kochar DK, Norris RL. *The Ebbinghaus retention curve: training does not increase the ability to apply pressure immobilisation in simulated snake bite – implications for snake bite first aid in the developing world.* Trans R Soc Trop Med Hyg 2008, 102:451-459

Snakebite – Tourniquet (First aid)

Question (PICO)	In humans with a snakebite (P) is a tourniquet (I) compared to no tourniquet (C) effective and feasible for laypersons as a first aid treatment to increase survival, tissue healing, functional recovery, pain, complications, time to resumption of usual activities, restoration to the pre-exposure condition, time to resolution of symptoms? (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "snake bites"] OR [mh "snake venoms"] OR snakebite*:ti,ab,kw OR 'snake bite':ti,ab,kw OR 'snake bites':ti,ab,kw OR 'snake envenomation':ti,ab,kw **MEDLINE** (via PubMed interface) for guidelines and systematic reviews using the following search strategy: 1. Snakebite[Mesh] OR "snake venoms"[Mesh] OR snakebite*[TIAB] OR "snake bite*"[TIAB] OR "snake envenomation*"[TIAB] 2. Bandage[Mesh] OR bandage*[TIAB] OR pressure[Mesh] OR pressure*[TIAB] OR immobilization[Mesh] OR immobili*[TIAB] OR tourniquet[Mesh] OR tourniquet*[TIAB] OR suction[Mesh] OR irrigation[Mesh] OR extract*[TIAB] OR suction*[TIAB] OR suck*[TIAB] OR aspirat*[TIAB] OR irrigat*[TIAB] OR ice[TIAB] OR cryotherapy[Mesh] OR cryotherapy[TIAB] OR cold[TIAB] 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Snakebite/exp 'snake venom'/exp OR snakebite*:ab,ti OR 'snake bite':ab,ti OR 'snake bites':ab,ti OR 'snake envenomation':ab,ti 2. 'Bandages and dressing'/exp OR bandage:ab,ti OR pressure/exp OR pressure*:ab,ti OR immobilization/exp OR immobili*:ab,ti OR tourniquet/de OR tourniquet*:ab,ti OR suction/exp OR 'wound irrigation'/exp OR extract*:ab,ti OR suction*:ab,ti OR suck*:ab,ti OR aspirat*:ab,ti OR irrigat*:ab,ti OR ice:ab,ti OR cryotherapy/exp OR cryotherapy:ab,ti OR cold:ab,ti 3. 1-2 AND

	Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface). Michael, 2011.
Search date	20 March 2015
In/Exclusion criteria	**Population**: Include: People with a snakebite. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Amaral, 1998, Brazil	Observational: cohort study	97 patients who presented to Hospital João XXIII in Belo Horizonte after being bitten by the South American rattlesnake. 16 females, 81 males, age range 3-88 years. Patients were divided in a tourniquet group (n=45) and a non-tourniquet group (n=52)	Tourniquet vs no tourniquet	
Madaki, 2005, Nigeria	Observational: cohort study	103 snake bite patients (62 males, 41 females), mean age 26.8±14.8 years (3-65 years) at Zamko Comprehensive Health Care centre between January and December 2001	Tourniquet vs no first aid	
Michael, 2011, Nigeria	Observational: cohort study	72 snake bite patients, mean age 23.4±15.7 years (0.75-90 years) at Zamko Comprehensive Health Care centre between April and July 2006	Tourniquet vs no first aid	A minimum sample size of 60 subjects was targeted, based on 80% power to detect a difference in

				complication rate with 95% confidence.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Number of deaths	Tourniquet vs no tourniquet	Not statistically significant: 2/45 vs 3/52 OR: 0.76, 95%CI [0.12; 4.76] (p=0.77)*¥	1, 45 vs 52 §	Amaral, 1998
Local oedema		Not statistically significant: 17/42 vs 21/51 OR: 0.97, 95%CI [0.42; 2.23] (p=0.95)*¥	1, 42 vs 51 §	
Acute renal failure		Not statistically significant: 4/42 vs 4/52 OR: 1.26, 95%CI [0.30; 5.38] (p=0.75)*¥	1, 42 vs 52 §	
Acute respiratory failure		Not statistically significant: 3/35 vs 3/49 OR: 1.44, 95%CI [0.27; 7.58] (p=0.67)*¥	1, 35 vs 49 §	
Envenoming	Tourniquet vs no first aid	Not statistically significant: 31/34 vs 16/19 OR: 1.94, 95%CI [0.35; 10.72] (p=0.45)*¥	1, 34 vs 19 §	Madaki, 2005
Necrosis		Not statistically significant: 3/38 vs 1/19 OR: 1.54, 95%CI [0.15; 15.91] (p=0.72)*¥	1, 38 vs 19 §	
Death or disability		Not statistically significant: 14/53 vs 1/15 OR: 5.03, 95%CI [0.60; 41.81] (p=0.14)*¥	1, 53 vs 15	Michael, 2011
Duration of hospital stay (days)	Tourniquet vs no tourniquet	Statistically significant: 4.6±2.0 vs 3.7±2.5 MD: 0.9 (p=0.04) *In favour of no tourniquet*	1, 53 vs 19	

Mean ± SD (unless otherwise indicated)

* Calculations done by the reviewer(s) using Review Manager software

¥ Imprecision (large variability of results)

§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations
Amaral, 1998	No	No	Yes	No	
Madaki, 2005	No	No	Yes	No	
Michael, 2011	No	No	Yes	No	

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/low number of events/large variability of the results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Conclusion	There is limited evidence from 3 observational studies, neither in favour of the intervention nor the control. A statistically significant decrease of number of deaths, local oedema, acute respiratory failure, acute renal failure, envenoming, necrosis or disability, using tourniquet compared to no tourniquet, could not be demonstrated (Amaral 1998, Madaki 2005, Michael 2011). Moreover, it was shown that tourniquet resulted in a statistically significant increase of duration of hospital stay, compared to no tourniquet in one study (Michael 2011). Evidence is of very low quality and results of these studies are imprecise due to limited sample size and large variability of results.
Reference(s)	**Articles** Amaral CFS, Campolina D, Dias MB, Bueno CM, Rezende NA. *Tourniquet ineffectiveness to reduce the severity of enevenoming after* Crotalus Durissus *snake bite in Belo Horizonte, Minas Gerais, Brazil*. Toxicon 1998, 36(5):805-808 Madaki JKA, Obilom RE, Mandon BM. *Pattern of First-Aid Measures Used by Snake-bite Patients and Clinical Outcome at Zamko Comprehensive Health Centre, Langtang, Plateau State*. Nigerian Medical Practitioner 2005, 48(1):10-13 Michael GC, Thacher TD, Shehu MIL. *The effect of pre-hospital care for venomous snake bite on outcome in Nigeria*. Transactions of the Royal Society of Tropical Medicine and Hygiene 2011, 105:95-101

Snakebite – Cryotherapy (First aid)

Question (PICO)	In humans with a snakebite (P) is cryotherapy (I) compared to no cryotherapy (C) effective and feasible for laypersons as a first aid treatment to increase survival, tissue healing, functional recovery, pain, complications, time to resumption of usual activities, restoration to the pre-exposure condition, time to resolution of symptoms? (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "snake bites"] OR [mh "snake venoms"] OR snakebite*:ti,ab,kw OR 'snake bite':ti,ab,kw OR 'snake bites':ti,ab,kw OR 'snake envenomation':ti,ab,kw **MEDLINE** (via PubMed interface) for guidelines and systematic reviews using the following search strategy: 1. Snakebite[Mesh] OR "snake venoms"[Mesh] OR snakebite*[TIAB] OR "snake bite*"[TIAB] OR "snake envenomation*"[TIAB] 2. Bandage[Mesh] OR bandage*[TIAB] OR pressure[Mesh] OR pressure*[TIAB] OR immobilization[Mesh] OR immobili*[TIAB] OR tourniquet[Mesh] OR tourniquet*[TIAB] OR suction[Mesh] OR irrigation[Mesh] OR extract*[TIAB] OR suction*[TIAB] OR suck*[TIAB] OR aspirat*[TIAB] OR irrigat*[TIAB] OR ice[TIAB] OR cryotherapy[Mesh] OR cryotherapy[TIAB] OR cold[TIAB] 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy:

	1. Snakebite/exp 'snake venom'/exp OR snakebite*:ab,ti OR 'snake bite':ab,ti OR 'snake bites':ab,ti OR 'snake envenomation':ab,ti 2. 'Bandages and dressing'/exp OR bandage:ab,ti OR pressure/exp OR pressure*:ab,ti OR immobilization/exp OR immobili*:ab,ti OR tourniquet/de OR tourniquet*:ab,ti OR suction/exp OR 'wound irrigation'/exp OR extract*:ab,ti OR suction*:ab,ti OR suck*:ab,ti OR aspirat*:ab,ti OR irrigat*:ab,ti OR ice:ab,ti OR cryotherapy/exp OR cryotherapy:ab,ti OR cold:ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	20 March 2015
In/Exclusion criteria	**Population**: Include: People with a snakebite. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Cohen, 1992, USA	Experimental: Randomized controlled trial	24 Sprague-Dawley rats were anesthetized and injected with 6.0 mg/kg venom from *Agkistrodon piscivorus* in the left upper hind leg. They were treated with heat (n=8), cold (n=8) or ambient temperature (n=8). Tissue injury score was measured = sum of individual ratings (scale 0-3) for epidermal necrosis, subcutaneous inflammation,	1. Heat: constant temperature water bath at 45°C 2. Cold: small plastic bag filled with ice placed on envenomated leg 3. Control: ambient temperature [Data for heat were not extracted]	

		vascular thrombosis or necrosis and myocytolysis.		

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Deaths before end of treatment	Cold vs control	Not statistically significant: 0 vs 1 OR: 0.29, 95%CI [0.01, 8.37] (p=0.47)*¥	1, 8 vs 8 §	Cohen, 1992
Tissue injury scores		Not statistically significant: 9.0 vs 8.5 (p≥0.05)		

Mean ± SD (unless otherwise indicated)

* Calculations done by the reviewer(s) using Review Manager software

¥ Imprecision (large variability of results)

§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Cohen, 1992	Yes	Yes	No	No	Animal study (indirectness)

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/lack of data/large variability of the results
Inconsistency	0	
Indirectness	-1	
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Conclusion	There is limited evidence from 1 experimental studies, neither in favour of the intervention nor the control. A statistically significant decrease of death or tissue score, using cold application compared to no treatment, could not be demonstrated (Cohen 1992). Evidence is of very low quality and results of this study are imprecise due to limited sample size, lack of data and/or large variability of results.
Reference(s)	**Articles** Cohen WR, Wetzel W, Kadish A. *Local heat and cold application after eastern cottonmouth moccasin (Agkistrodon piscivorus) envenomation in the rat: effect on tissue injury.* Toxicon 1992, 30(11):1383-1386

Snakebite – Irrigation/washing (First aid)

Question (PICO)	In humans with a snakebite (P) is irrigation/washing of the venom (I) compared to no irrigation/washing of the venom (C) effective and feasible for laypersons as a first aid treatment to increase survival, tissue healing, functional recovery, pain, complications, time to resumption of usual activities, restoration to the pre-exposure condition, time to resolution of symptoms? (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "snake bites"] OR [mh "snake venoms"] OR snakebite*:ti,ab,kw OR 'snake bite':ti,ab,kw OR 'snake bites':ti,ab,kw OR 'snake envenomation':ti,ab,kw **MEDLINE** (via PubMed interface) for guidelines and systematic reviews using the following search strategy: 1. Snakebite[Mesh] OR "snake venoms"[Mesh] OR snakebite*[TIAB] OR "snake bite*"[TIAB] OR "snake envenomation*"[TIAB] 2. Bandage[Mesh] OR bandage*[TIAB] OR pressure[Mesh] OR pressure*[TIAB] OR immobilization[Mesh] OR immobili*[TIAB] OR tourniquet[Mesh] OR tourniquet*[TIAB] OR suction[Mesh] OR irrigation[Mesh] OR extract*[TIAB] OR suction*[TIAB] OR suck*[TIAB] OR aspirat*[TIAB] OR irrigat*[TIAB] OR rins*[TIAB] OR wash*[TIAB] OR ice[TIAB] OR cryotherapy[Mesh] OR cryotherapy[TIAB] OR cold[TIAB] 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Snakebite/exp 'snake venom'/exp OR snakebite*:ab,ti OR 'snake bite':ab,ti OR 'snake bites':ab,ti OR 'snake envenomation':ab,ti 2. 'Bandages and dressing'/exp OR bandage:ab,ti OR pressure/exp OR pressure*:ab,ti OR immobilization/exp OR immobili*:ab,ti OR tourniquet/de OR tourniquet*:ab,ti OR suction/exp OR 'wound irrigation'/exp OR extract*:ab,ti OR suction*:ab,ti OR suck*:ab,ti OR aspirat*:ab,ti OR irrigat*:ab,ti OR ice:ab,ti OR cryotherapy/exp OR cryotherapy:ab,ti OR cold:ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	20 March 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched.

	An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Snakebite – Suction (First aid)

Question (PICO)	In humans with a snakebite (P) is suction of the venom (I) compared to no suction of the venom (C) effective and feasible for laypersons as a first aid treatment to increase survival, tissue healing, functional recovery, pain, complications, time to resumption of usual activities, restoration to the pre-exposure condition, time to resolution of symptoms? (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "snake bites"] OR [mh "snake venoms"] OR snakebite*:ti,ab,kw OR 'snake bite':ti,ab,kw OR 'snake bites':ti,ab,kw OR 'snake envenomation':ti,ab,kw **MEDLINE** (via PubMed interface) using the following search strategy: 1. Snakebite[Mesh] OR "snake venoms"[Mesh] OR snakebite*[TIAB] OR "snake bite*"[TIAB] OR "snake envenomation*"[TIAB] 2. Bandage[Mesh] OR bandage*[TIAB] OR pressure[Mesh] OR pressure*[TIAB] OR immobilization[Mesh] OR immobili*[TIAB] OR tourniquet[Mesh] OR tourniquet*[TIAB] OR suction[Mesh] OR irrigation[Mesh] OR extract*[TIAB] OR suction*[TIAB] OR suck*[TIAB] OR aspirat*[TIAB] OR irrigat*[TIAB] OR ice[TIAB] OR cryotherapy[Mesh] OR cryotherapy[TIAB] OR cold[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Snakebite/exp 'snake venom'/exp OR snakebite*:ab,ti OR 'snake bite':ab,ti OR 'snake bites':ab,ti OR 'snake envenomation':ab,ti 2. 'Bandages and dressing'/exp OR bandage:ab,ti OR pressure/exp OR pressure*:ab,ti OR immobilization/exp OR immobili*:ab,ti OR tourniquet/de OR tourniquet*:ab,ti OR suction/exp OR 'wound irrigation'/exp OR extract*:ab,ti OR suction*:ab,ti OR suck*:ab,ti OR aspirat*:ab,ti OR irrigat*:ab,ti OR ice:ab,ti OR cryotherapy/exp OR cryotherapy:ab,ti OR cold:ab,ti

	3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in MEDLINE (via PubMed interface)
Search date	20 March 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Michael, 2011, Nigeria	Observational: cohort study	72 snake bite patients, mean age 23.4±15.7 years (0.75-90 years) at Zamko Comprehensive Health Care centre between April and July 2006	Suction vs no first aid	A minimum sample size of 60 subjects was targeted, based on 80% power to detect a difference in complication rate with 95% confidence.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Death or disability	Suction vs no first aid	Not statistically significant: 0/3 vs 1/15 OR: 1.38, 95%CI [0.05; 41.66] (p=0.85)* ¥	1, 3 vs 15 §	Michael, 2011

Mean ± SD (unless otherwise indicated)

* Calculations done by the reviewer(s) using Review Manager software

¥ Imprecision (large variability of results)

§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations
Michael	No	No	Yes	No	

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Low number of events/large variability of the results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Conclusion	There is limited evidence from 1 observational study, neither in favour of the intervention nor the control. A statistically significant decrease of deaths or disability, using suction compared to no first aid, could not be demonstrated (Michael 2011). Evidence is of very low quality and results of this study are imprecise due to limited sample size and large variability of results.
Reference(s)	**Articles** Michael GC, Thacher TD, Shehu MIL. *The effect of pre-hospital care for venomous snake bite on outcome in Nigeria*. Transactions of the Royal Society of Tropical Medicine and Hygiene 2011, 105:95-101

Dog bite – Wound irrigation (First aid)

Question (PICO)	In humans with a dog bite (P) is wound irrigation (I) compared to not doing this (C) effective as a first aid treatment to increase tissue healing, functional recovery, pain, complications, restoration to the pre-exposure condition, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: (dog NEXT bite*):ti,ab,kw OR (cat NEXT bite*):ti,ab,kw OR (human NEXT bite*):ti,ab,kw **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Bites and Stings"[Mesh] OR bite*[TIAB] 2. "Cats"[Mesh] OR "Dogs"[Mesh] OR "Humans"[Mesh] OR cat[TIAB] OR cats[TIAB] OR dog*[TIAB] or human*[TIAB] 3. cleans*[TIAB] OR irrigat*[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'bites and stings'/exp OR bite*:ab,ti 2. 'cat'/exp OR 'dog'/exp OR 'human'/exp OR cat:ab,ti OR cats:ab,ti OR dog*:ab,ti OR human*:ab,ti 3. Cleans*:ab,ti OR irrigate*:ab,ti 4. 1-3 AND
Search date	2 July 2015
In/Exclusion criteria	**Population**: Include: people with dog bites **Intervention**: Include: wound irrigation with water or another fluid/disinfectant **Outcome**: Include: infection

	Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion(s)	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Dog bite – Educational interventions to children (Prevention)

Question (PICO)	In humans (P) is education to children (I) compared to no educational programmes effective to prevent dog bites (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: (dog NEXT bite*):ti,ab,kw **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Bites and Stings"[Mesh] OR bite*[TIAB] 2. "Dogs"[Mesh] OR dog*[TIAB] 3. "Accident Prevention"[Mesh] OR "Primary Prevention"[Mesh:NoExp] OR "Health Education"[Mesh] OR "Health Behavior"[Mesh:NoExp] OR "Preventive Medicine"[Mesh] OR "Prevention and control "[Subheading] 4. 1-3 AND [limits: 2009-2015] **Embase** (via Embase.com interface) using the following search strategy: 1. 'bites and stings'/exp OR bite*:ab,ti 2. 'dog'/exp OR dog*:ab,ti 3. 'prevention'/exp OR 'health education'/exp OR 'health behavior'/exp OR 'preventive medicine'/exp OR *'prevention':lnk* 4. 1-3 AND [limits: 2009-2015]

	Guidelines, systematic reviews, retrieved with the above searches, and used as source for individual studies: Duperrex, 2009 Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	2 July 2015
In/Exclusion criteria	**Population**: Include: children or mix of adults and children **Intervention**: Include: education aimed at preventing dog bites **Outcome**: Include: prevention of dog bites, decreased incidence of dog bites Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Chapman, 2000	Experimental: randomized controlled trial	346 children (197 intervention, 149 control) 7-8 years old from 8 primary schools in metropolitan Sydney (4 intervention, 4 control)	1. Intervention group: one 30-minute lesson of Prevent-a-Bite by an accredited dog handler (explanation, demonstration and practice: patting the dog + precautionary and protective body posture). 2. Control group: no intervention.	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Inappropiate behavior in the presence of a dog	One 30 min lesson on dog bite prevention to 7-8 y old children vs no intervention	Statistically significant: Crude data (no ICC): 18/197 vs 118/149 § OR: 0.03 95% CI [0.01;0.05] (p<0.05) Calculated ICC: 1/8 vs 5/6 § OR: 0.03 95%CI [0.00;0.57] (p<0.05)	1, 197 vs 149	Chapman, 2000

§ Imprecision (low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Chapman, 2000	Unclear	Yes (for outcome concerning behaviour)	Yes	Unclear	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Low number of events
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion(s)	There is limited evidence in favour of education on dog prevention to children. It was shown that a 30 min lesson on dog bite prevention to 7-8 y old children resulted in a statistically significant decrease of inappropriate behaviour in the presence of a dog (Chapman 2000). Evidence is of low quality and results cannot be considered precise due to limited sample size, lack of data and/or large variability of results.
Reference(s)	**Articles** Chapman S, Cornwall J, Righetti J, Sung L. *Preventing dog bites in children: randomised controlled trial of an educational intervention*. BMJ 2000, 320(7248):1512–3 **Systematic reviews** Duperrex O, Blackhall K, Burri M, Jeannot E. *Education of children and adolescents for the prevention of dog bite injuries*. Cochrane Database Syst Rev 2009, CD004726.

Dog bite – Risk factors

Question (PICO)	In humans (P) which risk factors exist (RF) resulting in dog bites (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: (dog NEXT bite*):ti,ab,kw **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Bites and Stings"[Mesh] OR bite*[TIAB] 2. "Dogs"[Mesh] OR dog*[TIAB] 3. "Risk Factors"[Mesh] OR risk factor*[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'bites and stings'/exp OR bite*:ab,ti 2. 'dog'/exp OR dog*:ab,ti 3. 'risk factor'/exp OR (Risk NEXT/1 factor*):ab,ti 4. 1-3 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in MEDLINE (via PubMed interface).
Search date	2 July 2015
In/Exclusion criteria	**Population**: Include: adults and children

	Intervention: Include: modifiable, proximal risk factor with a potential immediate implication for practice that results in primary prevention at the household or community level. Risk factors related to healthy persons. Exclude: risk factors that lead to interventions with already proven effectiveness. The risk factor that does not precede the outcome. The risk factor is common sense. **Outcome**: Include: dog bites Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, cross sectional study, and the data are available. Exclude: case series, animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Risk factor	Remarks
Gershman, 1994, USA	Observational: case-control study	178 biting dogs were identified from the Denver Municipal Animal Shelter for a first-bite episode of a non-household member in which the victim received medical treatment. 178 control dogs were identified by calling neighbouring households	Exposure information was gathered through structured telephone interviews: Dog's characteristics, house and outdoor environment, discipline and training, behaviour and owner's dog rearing practices	
Messam, 2008, USA	Observational: cross sectional study	Among clients in the waiting room of veterinary clinics, owners of dogs biting (not during play, 161) and not biting (951) were selected	Exposure information was gathered through interviewing clients in the waiting room of veterinary clinics: respondents characteristics, canine characteristics, factors related to owner-dog habitual interactions, and factors related to the dogs' living environment	Except for three age time-related questions, all responses were categorical.
Messam, 2012, USA	Observational: cross sectional study	Among clients in the waiting room of veterinary clinics, owners of dogs biting (during play, 110) and not biting (951) were selected	Same as Messam, 2008	

Synthesis of findings

Outcome	Comparison	Effect Size £	#studies, # participants	Reference
Risk of non-play dog bite	Not neutered vs neutered	Statistically significant: aOR: 2.6, 95%CI [1.1;6.3] (p<0.05) *In favour of not neutering the dog as a risk factor*	1, 178 vs 178	Gershman, 1994
	Chained while in yard vs not chained while in yard	Not statistically significant: aOR: 2.8, 95%CI [1.0;8.1] ¥ (p>0.05)		
	No obedience school vs obedience school	Not statistically significant: aOR: 1.9, 95%CI [0.7;4.9] ¥ (p>0.05)		
	Dog in house 19-24 h/day vs not	Statistically significant: aRR: 1.97, 95%CI [1.17;3.32] (p<0.05) *In favour of dog in the house 19-24 h/day as a risk factor*	1, 161 vs 951	Messam, 2008
	Sleep in family member's bedroom vs not	Statistically significant: Region 1: aRR: 2.54, 95%CI [1.43;4.54] (p<0.05) *In favour of dog sleeping in the family member's bedroom as a risk factor* Not statistically significant: Region 2: aRR: 1.11, 95%CI [0.67;1.85] ¥ (p>0.05)		
	Dog chained 1-24 h/day vs not	Not statistically significant: aRR: 1.15, 95%CI [0.66;1.99] ¥ (p>0.05)		
	Dog locked up 1-6 h/day vs not	Statistically significant: aRR: 1.71, 95%CI [1.02;2.86] (p<0.05) *In favour of dog lock up 1-6 h/day as a risk factor*		
	Can leave premises unaccompanied vs cannot leave premises unaccompanied	Not statistically significant: Region 1: aRR: 1.04, 95%CI [0.63;1.72] (p>0.05) Statistically significant: Region 2: aRR: 3.40, 95%CI [1.98;5.85] (p<0.05) *In favour of being able to leave premises unaccompanied as a risk factor*		
	Dog allowed into presence of strangers vs not	Statistically significant: aRR: 1.77, 95%CI [1.03;3.04] (p<0.05) *In favour of allowing the dog into presence of strangers as a risk factor*		

	Dog not removed/allowed to retreat when fearful vs dog removed/allowed to retreat when fearful	Statistically significant: aRR: 1.71, 95%CI [1.06;2.76] (p<0.05) *In favour of not removing the dog or allow the dog to retreat when fearful as a risk factor*		
Risk of bite during play	Dog in house 19-24 h/day vs not	Statistically significant: aRR: 3.40, 95%CI [1.59;7.28] (p<0.05) *In favour of dog in the house 19-24 h/day as a risk factor*	1, 110 vs 951	Messam, 2012
	Sleep in family member's bedroom vs not	Not statistically significant: aRR: 1.04, 95%CI [0.70;1.56] ¥ (p>0.05)		
	Dog chained 1-24 h/day vs not	Statistically significant: aRR: 2.34, 95%CI [1.45;3.77] (p<0.05) *In favour of dog being chainied 1-24 h/day as a risk factor*		
	Dog locked up 1-6 h/day vs not	Statistically significant: aRR: 3.31, 95%CI [2.06;5.32] (p<0.05) *In favour of dog being locked up 1-6 h/day as a risk factor*		
	Can leave premises unaccompanied vs cannot leave premises unaccompanied	Statistically significant: aRR: 2.57, 95%CI [1.56;4.24] (p<0.05) *In favour of being able to leave premises unaccompanied as a risk factor*		
	Dog allowed into presence of strangers vs not	Not statistically significant: aRR: 1.37, 95%CI [0.79;2.40] ¥ (p>0.05)		
	Dog not removed/allowed to retreat when fearful vs dog removed/allowed to retreat when fearful	Statistically significant: aRR: 1.97, 95%CI [1.15;3.38] (p<0.05) *In favour of not removing the dog or allow the dog to retreat when fearful as a risk factor*		

¥ Imprecision (large variability of results)

Quality of evidence

Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations
Gershman, 1994	No	No	No	No	
Messam, 2008	No (similar respondent and dog characteristics for bite and non-bite group)	No (only possible via questionnaire)	No	No	
Messam, 2012	No	No	No	No	

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Large variability of results for some risk factors
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Conclusion(s)	It was shown that not neutering the dog, keeping the dog in house 19-24 h/day, letting the dog sleep in a family member's bedroom, locking the dog up 1-6 h/day, letting the dog leave the premises unaccompanied, allowing the dog into the presence of strangers and not removing the dog or allowing it to retreat when fearful resulted in a statistically significant increased risk of **non-play dog bites** (Messam 2008, Gershman 1994). However, a statistically significant increased risk of chaining the dog in the yard, not going to obedience school and keeping the dog chained 1-24h/day on non-play dog bites, could not be demonstrated (Gersham 1994, Messam 2008). It was shown that keeping the dog in house 19-24 h/day, locking the dog up 1-6 h/day, letting the dog leave the premises unaccompanied, letting the dog chained 1-24 h/day and not removing the dog or allowing it to retreat when fearful resulted in a statistically significant increased risk of **dog bites during play** (Messam 2012). However, a statistically significant increased risk of letting the dog sleep in a family member's bedroom and allowing the dog in the presence of strangers on dog bites during play, could not be demonstrated (Messam 2012). Evidence is of very low quality and results cannot be considered precise due to large variability of results.
Reference(s)	**Articles** Gershman KA, Sacks JJ, Wright JC. *Which dogs bite? A case-control study of risk factors*. Pediatrics 1994, 93:913-7 Messam LL, Kass PH, Chomel BB, Hart LA. *Risk factors for dog bites occurring during and outside of play: are they different?* Prev Vet Med 2012, 107(1-2):110-20 Messam LL, Kass PH, Chomel BB, Hart LA. *The human-canine environment: a risk factor for non-play bites?* Vet J. 2008, 177(2):205-15

Human bite – Wound irrigation (First aid)

Question (PICO)	In humans with a human bite (P) is wound irrigation (I) compared to not doing this (C) effective as a first aid treatment to increase tissue healing, functional recovery, pain, complications, restoration to the pre-exposure condition, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: (dog NEXT bite*):ti,ab,kw OR (cat NEXT bite*):ti,ab,kw OR (human NEXT bite*):ti,ab,kw **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Bites and Stings"[Mesh] OR bite*[TIAB] 2. "Cats"[Mesh] OR "Dogs"[Mesh] OR "Humans"[Mesh] OR cat[TIAB] OR cats[TIAB] OR dog*[TIAB] or human*[TIAB] 3. cleans*[TIAB] OR irrigat*[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy:

	1. 'bites and stings'/exp OR bite*:ab,ti 2. 'cat'/exp OR 'dog'/exp OR 'human'/exp OR cat:ab,ti OR cats:ab,ti OR dog*:ab,ti OR human*:ab,ti 3. Cleans*:ab,ti OR irrigat*:ab,ti 4. 1-3 AND
Search date	2 July 2015
In/Exclusion criteria	**Population**: Include: people with human bites **Intervention**: Include: wound irrigation with water or another fluid/disinfectant **Outcome**: Include: infection Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion(s)	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Cat scratch or bite – Wound irrigation (First aid)

Question (PICO)	In humans with a cat scratch or bite (P), is wound irrigation (I) compared to not doing this (C) effective as a first aid treatment to increase tissue healing, functional recovery, pain, complications, restoration to the pre-exposure condition, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: (dog NEXT bite*):ab,ti OR (cat NEXT bite*):ab,ti OR (human NEXT bite*):ab,ti **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Bites and Stings"[Mesh] OR bite*[TIAB] 2. "Cats"[Mesh] OR "Dogs"[Mesh] OR "Humans"[Mesh] OR cat[TIAB] OR cats[TIAB] OR dog*[TIAB] or human*[TIAB] 3. cleans*[TIAB] OR irrigat*[TIAB] 4. 1-3 AND

	Embase (via Embase.com interface) using the following search strategy: 1. 'bites and stings'/exp OR bite*:ab,ti 2. 'cat'/exp OR 'dog'/exp OR 'human'/exp OR cat:ab,ti OR cats:ab,ti OR dog*:ab,ti OR human*:ab,ti 3. Cleans*:ab,ti OR irrigat*:ab,ti 4. 1-3 AND
Search date	2 July 2015
In/Exclusion criteria	**Population**: Include: people with a cat scratch or bite **Intervention**: Include: wound irrigation with water or another fluid/disinfectant **Outcome**: Include: infection Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion(s)	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Cat bite or scratch – Risk factors

Question (PICO)	In humans (P) which risk factors exist (RF) resulting in cat bites or scratches (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: (cat NEXT bite*):ti,ab,kw **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Bites and Stings"[Mesh] OR bite*[TIAB] OR scratch*[TIAB] 2. "Cats"[Mesh] OR cat[TIAB] OR cats[TIAB] 3. "Risk Factors"[Mesh] OR risk factor*[TIAB] 4. 1-3 AND

	Embase (via Embase.com interface) using the following search strategy: 1. 'bites and stings'/exp OR bite*:ab,ti OR scratch*:ab,ti 2. 'cat'/exp OR cat:ab,ti OR cats:ab,ti 3. 'risk factor'/exp OR (Risk NEXT/1 factor*):ab,ti 4. 1-3 AND
Search date	3 July 2015
In/Exclusion criteria	**Population**: Include: adults and children **Intervention**: Include: modifiable, proximal risk factor with a potential immediate implication for practice that results in primary prevention at the household or community level. Risk factors related to healthy persons. Exclude: risk factors that lead to interventions with already proven effectiveness. The risk factor that does not precede the outcome. The risk factor is common sense. **Outcome**: Include: cat bites or scratches Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion(s)	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Jellyfish sting – Salt water (First aid)

Question (PICO)	In humans with a jellyfish sting (P), does rinsing with salt water (I) compared to not rinsing with salt water or another intervention (C) increase survival, tissue healing, functional recovery, pain, complications, time to resumption of usual activities, restoration to the pre-exposure condition and time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "jellyfish"] OR [mh Scyphozoa] OR [mh Cubozoa] OR [mh "Cnidarian venoms"] OR jellyfish:ti,ab,kw OR Scyphozoa:ti,ab,kw OR Cubozoa:ti,ab,kw OR "Cnidarian venom*":ti,ab,kw

	MEDLINE (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Scyphozoa"[Mesh] OR "Cubozoa"[Mesh] OR "Cnidarian Venoms"[Mesh] OR jellyfish[TIAB] OR Scyphozoa[TIAB] OR Cubozoa[TIAB] OR "Cnidarian Venom*"[TIAB] 2. "Acetic Acid"[Mesh] OR vinegar[TIAB] OR "acetic acid"[TIAB] OR "hot water"[TIAB] OR "warm water"[TIAB] OR "salt water"[TIAB] OR seawater[Mesh] OR "seawater"[TIAB] OR "saline"[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'jellyfish'/exp OR 'Cubozoa'/exp OR 'jellyfish sting'/exp OR jellyfish:ab,ti OR Cubozoa:ab,ti OR Scyphozoa:ab,ti OR "Cnidarian venom":ab,ti 2. 'vinegar'/exp OR vinegar:ab,ti OR 'acetic acid':ab,ti OR 'sea water'/exp OR seawater:ab,ti OR 'sea water':ab,ti OR 'hot water'/exp OR 'hot water':ab,ti OR 'warm water':ab,ti 3. 1-2 AND Guidelines, systematic reviews, retrieved with the above searches, and used as source for individual studies: Li, 2013 Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface). Honeycutt, 2014
Search date	07 April 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Thomas, 2001, USA	Experimental: Quasi-randomised controlled trial	63 participants, aged >7 years accidentally stung by *Carybdea alata*	1. Vinegar and fresh water 2. Vinegar and seawater 3. Vinegar and sting-aid 4. Vinegar and Adolph's meat tenderiser All interventions were sprayed for 15 minutes	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Pain (100 mm VAS)	Seawater vs fresh water	5 min after treatment: Not statistically significant: 28.1±19.46 vs 34.5±19.52 MD: -6.40, 95%CI [-20.01, 7.21] (p=0.36)*¥	1, 14 vs 18 §	Thomas, 2001
		10 min after treatment: Not statistically significant: 35.2±24 vs 40.7±24.90 MD: -5.50, 95%CI [-28.81, 17.81] (p=0.64)*¥	1, 9 vs 8 §	
	Seawater vs Sting-aid	5 min after treatment: Not statistically significant: 28.1±19.46 vs 35.3±19.47 MD: -7.20, 95%CI [-21.89, 7.29] (p=0.34)*¥	1, 14 vs 13 §	
		10 min after treatment: Not statistically significant: 35.2±24 vs 32.8±23.70 MD: 2.40, 95%CI [-19.64, 24.44] (p=0.83)*¥	1, 9 vs 9 §	
	Seawater vs Adolphs's meat tenderiser	5 min after treatment: Not statistically significant: 28.1±19.46 vs 36.9±19.24 MD: -8.80, 95%CI [-24.07, 6.47] (p=0.26)*¥	1, 14 vs 11 §	
		10 min after treatment: Not statistically significant: 35.2±24 vs 38.6±24.25 MD: -3.40, 95%CI [-28.35, 21.55] (p=0.79)*¥	1, 9 vs 6 §	
Cessation of pain	Seawater vs fresh water	Not statistically significant: 6/16 vs 5/19 OR: 1.68, 95%CI [0.40, 7.07] (p=0.48)¥	1, 16 vs 19 §	
	Seawater vs Sting-aid	Not statistically significant: 6/16 vs 3/13 OR: 2.00, 95%CI [0.39, 10.31] (p=0.41)*¥	1, 16 vs 13 §	
	Seawater vs Adolphs's meat tenderiser	Not statistically significant: 6/16 vs 2/14 OR: 3.60, 95%CI [0.59, 21.93] (p=0.16)*¥	1, 16 vs 14 §	

Mean ± SD (unless otherwise indicated)

* Calculations done by the reviewer(s) using Review Manager software

¥ Imprecision (large variability of results)

§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Thomas, 2001	Yes, researcher grabbed in container in which spray bottles with treatments is available	No, treatments were in unmarked opaque spray bottles	No, adequately described	Yes, criteria for measuring the binary outcome were changed after the trial was completed	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/ large variability of the results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is limited evidence from 1 experimental study, neither in favour of the intervention nor the control. A statistically significant decrease of pain, using salt water compared to fresh water, sting-aid or Adolph's meat tenderiser, could not be demonstrated (Thomas, 2001). Evidence is of low quality and results of this study are imprecise due to limited sample size and/or large variability of results.
Reference(s)	**Articles** Thomas CS, Scott SA, Galanis DJ, Goto RS. *Box Jellyfish (*Carybdea alata*) in Waikiki. The analgesic effect of Sting-Aid, Adolph's meat tenderizer and fresh water on their stings: a double-blinded, randomized, placebo-controlled clinical trial*. Hawaii Medical Journal 2001, 60:205-210 **Systematic reviews** Li L, McGee RG, Isbister G, Webster AC. *Interventions for the symptoms and signs resulting from jellyfish stings*. Cochrane Database of Systematic Reviews 2013, Issue 12 Art No.: CD009688.

Jellyfish sting – Hot water (First aid)

Question (PICO)	In humans with a jellyfish sting (P), does hot water or hot packs (I) compared to no hot water or cold/ice (C) increase survival, tissue healing, functional recovery, pain, complications, time to resumption of usual activities, restoration to the pre-exposure condition and time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "jellyfish"] OR [mh Scyphozoa] OR [mh Cubozoa] OR [mh "Cnidarian veno ms"] OR jellyfish:ti,ab,kw OR Scyphozoa:ti,ab,kw OR Cubozoa:ti,ab,kw OR "Cnidarian venom*":ti,ab,kw **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Scyphozoa"[Mesh] OR "Cubozoa"[Mesh] OR "Cnidarian Venoms"[Mesh] OR jellyfish[TIAB] OR Scyphozoa[TIAB] OR Cubozoa[TIAB] OR "Cnidarian Venom*"[TIAB]

	2. "Acetic Acid"[Mesh] OR vinegar[TIAB] OR "acetic acid"[TIAB] OR "hot water"[TIAB] OR "warm water"[TIAB] OR "salt water"[TIAB] OR seawater[Mesh] OR "seawater"[TIAB] OR "saline"[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'jellyfish'/exp OR 'Cubozoa'/exp OR 'jellyfish sting'/exp OR jellyfish:ab,ti OR Cubozoa:ab,ti OR Scyphozoa:ab,ti OR "Cnidarian venom":ab,ti 2. 'vinegar'/exp OR vinegar:ab,ti OR 'acetic acid':ab,ti OR 'sea water'/exp OR seawater:ab,ti OR 'sea water':ab,ti OR 'hot water'/exp OR 'hot water':ab,ti OR 'warm water':ab,ti 3. 1-2 AND Guidelines, systematic reviews, retrieved with the above searches, and used as source for individual studies: Li, 2013 Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface). Honeycutt, 2014
Search date	07 April 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Loten, 2006, Australia	Experimental: Randomised controlled trial	96 participants, aged >8 years presenting with stings from *Physalia* (Bluebottle) jellyfish.	1. Hot water (45°C) via hose to truncal stings or bucket immersion for limb stings for 20 minutes	

		Hot water (n=49) vs ice pack (n=47)	2. Ice pack (-4°C) application for as long as tolerable within a 20-min period	
Nomura, 2002, USA	Experimental: Randomised controlled trial (within subjects)	30 healthy unpaid adult volunteers (physicians, nurses, clinical assistants, medical students) Subjects were stung on ventral surface of both mid-forearms with tentacles of *Carybdea alata*. Both tentacles were simultaneously applied on the forearm.	1. Hot fresh water (40-41°C): immersion for 20 minutes 2. Comparison: vinegar (5% acetic acid) or papain meat tenderizer (Adolph's meat tenderizer [Adolph's, Trumbull, CT] and water in a 4:1 ratio volume) for 20 minutes	
Thomas, 2001, USA	Experimental: Quasi-randomised controlled trial	133 participants stung by *Carybdea alata*	1. Vinegar and chemical hot packs (max. 43°C) 2. Vinegar and chemical cold packs (min 5.5°C) 3. Vinegar and air temperature packs All interventions were applied for 15 minutes	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Pain (VAS) (mm)	Hot water vs ice pack	Statistically significant: 54±22 vs 42±22 MD: 12.00, 95%CI [3.20; 20.80] (p=0.008) *In favour of hot water*	1, 49 vs 47 §	Loten, 2006
	Hot vs cold pack	At 5 min: Not statistically significant: 31.3±9.29 vs 32.8±9.07 MD: -1.50, 95%CI [-5.38; 2.38] (p=0.45)*	1, 44 vs 42 §	Thomas, 2001
		At 10 min: Statistically significant: 27.5±13.61 vs 36.2±13.36 MD: -8.70, 95%CI [-14.22; -2.18] (p=0.009)*	1, 35 vs 31 §	
		At 15 min: Not statistically significant: 34.1±18.01 vs 45.0±17.73 MD: -10.90, 95%CI [-24.13; 2.33] (p=0.11)*	1, 12 vs 17 §	
	Hot vs neutral pack	At 5 min: Statistically significant: 31.3±9.29 vs 37.7±8.96 MD: -6.40, 95%CI [-10.28; -2.52] (p=0.001)*	1, 44 vs 41 §	
		At 10 min: Statistically significant: 27.5±13.61 vs 38.2±13.41 MD: -10.70, 95%CI [-17.08; -4.32] (p=0.001)*	1, 35 vs 34 §	
		At 15 min:	1, 12 vs 14 §	

		Not statistically significant: 34.1±18.01 vs 37.3±17.96 MD: -3.20, 95%CI [-17.07; 10.67] (p=0.65)*		
Pain cessation	Hot vs cold pack	Not statistically significant: 18/44 vs 14/42 OR: 1.38, 95%CI [0.57; 3.34] (p=0.47)* ¥	1, 44 vs 42 §	
	Hot vs neutral pack	Not statistically significant: 18/44 vs 12/41 OR: 1.67, 95%CI [0.68; 4.12] (p=0.26)* ¥	1n 44 vs 41 §	
Clinically reduced pain at 10 minutes after treatment	Hot water vs ice pack	<u>Statistically significant:</u> 26/49 vs 15/47 RR: 1.66, 95%CI [1.01; 2.72] (p=0.04)* *In favour of hot water*	1, 49 vs 47 §	Loten, 2006
Clinically reduced pain at 20 minutes after treatment		<u>Statistically significant:</u> 39/45 vs 14/43 RR: 2.66, 95%CI [1.71; 4.15] (p<0.0001)* *In favour of hot water*	1, 45 vs 43 §	
Maximum Pain score (VAS) during 20 minute study (cm)	Comparison vs hot water	Not statistically significant: 4.4 vs 4.1 MD: 0.3 (p=0.047)	1, 25 vs 25§ (within subjects)	Nomura, 2002
Pain at t=4 min (cm)		<u>Statistically significant:</u> a. vs 2.1 MD: 1.1, 95%CI [0.6; 1.6] (p<0.001) *In favour of hot water*		
Pain at t=20 min (cm)		<u>Statistically significant:</u> 1.8 vs 0.2 MD: 1.6, 95%CI [0.9; 2.3] (p<0.001) *In favour of hot water*		
Visibly worse appearance after treatment		<u>Statistically significant:</u> 5/25 vs 16/25 RR: 0.31, 95%CI [0.14; 0.72] (p=0.0065) *In favour of hot water*		
Itchiness 24 h or later	Hot water vs ice pack	Not statistically significant: 18/42 vs 17/41 RR: 1.03, 95%CI [0.62; 1.71] (p=0.90)*¥	1, 42 vs 41 §	Loten, 2006
Red mark or minor rash 24 h or later		Not statistically significant: 18/42 vs 17/41 RR: 1.03, 95%CI [0.62; 1.71] (p=0.90)*¥		
Raised and red/wheal reaction 24 h or later		Not statistically significant: 8/42 vs 11/41 RR: 0.71, 95%CI [0.32; 1.58] (p=0.40)*¥		
Bulleous reaction 24 h or later		Not statistically significant: 1/42 vs 1/41 RR: 0.98, 95%CI [0.06; 15.09] (p=0.99)*¥		

Mean ± SD (unless otherwise indicated)
* Calculations done by the reviewer(s) using Review Manager software
¥ Imprecision (large variability of results)
§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Loten, 2006	No, computer generated randomisation list + sealed envelopes	Yes, but not possible	No, adequately described	Yes, no mention of persistant pain in follow-up	Potentially early stopping bias ("trial was stopped at the halfway interim analysis because hot water immersion was shown to be effective at 20 minutes")
Nomura, 2002	Unclear, not stated	Yes, but not possible	No, adequately described	Yes, individual data not mentioned, results of cross-over treatments not mentioned	
Thomas, 2001	Yes, packs randomly chosen from large container	Yes, but not possible	No, adequately described	Yes, criteria for measuring binary outcome (pain cessation) were changed after completion of trial	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/ large variability of the results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	**Pain:** There is limited evidence from 3 experimental studies in favour of heat. It was shown that hot water or a hot pack resulted in a statistically significant decrease of pain, compared to icepack, vinegar or papain meat tenderizer (Loten 2006, Nomura 2002, Thomas 2001). However, a difference in pain cessation could not be demonstrated (Thomas 2001). Evidence is of low quality and results cannot be considered precise due to limited sample size. **Dermatological outcomes:** There is limited evidence from 2 experimental studies, neither in favour of the intervention nor the control. A statistically significant decrease of itchiness, red mark or minor rash, raised and red/wheal reaction or bulleous reaction, using hot water compared to icepack, vinegar or papain meat tenderizer, could not be demonstrated (Loten 2006, Nomura 2002). Evidence is of low quality and results of these studies are imprecise due to limited sample size and/or large variability of results.
Reference(s)	**Articles**

	Loten C, Stokes B, Worsley D, Seymour JE, Jiang S, Isbister GK. *A randomised controlled trial of hot water (45°C) immersion versus ice packs for pain relief in bluebottle stings*. Med J Aust 2006, 184(7):329-33 Nomura JT, Sato RL, Ahern RM, Snow JL, Kuwaye TT, Yamamoto LG. *A randomized paired comparison trial of cutaneous treatments of acute jellyfish (*Carybdea alata*) stings.* Am J Emerg Med 2002, 20(7):624-6 Thomas CS, Scott SA, Galanis DJ, Goto RS. *Box jellyfish (*Carybdea alata*) in Waikiki: their influx cycle plus the analgesic effect of hot and cold packs on their stings to swimmers at the beach: a randomized, placebo-controlled, clinical trial*. Hawaii Medical Journal 2001, 60:100-107 **Systematic reviews** Li L, McGee RG, Isbister G, Webster AC. *Interventions for the symptoms and signs resulting from jellyfish stings*. Cochrane Database of Systematic Reviews 2013, Issue 12 Art No.: CD009688.

Jellyfish sting – Removing tentacles (First aid)

Question (PICO)	In humans with jellyfish stings (P), is removing the tentacle (I) compared to not removing the tentacle (C) effective as a first aid treatment to increase tissue healing, functional recovery, pain, complications, restoration to the pre-exposure condition, time to resolution of symptoms, deactivation of the venom (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "jellyfish"] OR [mh Scyphozoa] OR [mh Cubozoa] OR [mh "Cnidarian veno ms"] OR jellyfish:ti,ab,kw OR Scyphozoa:ti,ab,kw OR Cubozoa:ti,ab,kw OR "Cnidarian venom*":ti,ab,kw **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Scyphozoa"[Mesh] OR "Cubozoa"[Mesh] OR "Cnidarian Venoms"[Mesh] OR jellyfish[TIAB] OR Scyphozoa[TIAB] OR Cubozoa[TIAB] OR "Cnidarian Venom*"[TIAB] 2. Remov*[TIAB] OR extract*[TIAB] 3. Tentacle*[TIAB] OR nematocyst*[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'jellyfish'/exp OR 'Cubozoa'/exp OR 'jellyfish sting'/exp OR jellyfish:ab,ti OR Cubozoa:ab,ti OR Scyphozoa:ab,ti OR "Cnidarian venom":ab,ti 2. Remov*:ab,ti OR extract*:ab,ti 3. Tentacle*:ab,ti OR nematocyst*:ab,ti 4. 1-3 AND
Search date	28 July 2015
In/Exclusion criteria	**Population** Include: people with jellyfish stings **Intervention** Include: removal of tentacles with a credit card, safety razor, knife edge. **Comparison** Include: not removing the tentacle. **Outcome** Include: discharge, pain, functional recovery. Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available.

	An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Jellyfish sting – Vinegar (First aid)

Question (PICO)	In humans with a jellyfish sting (P), does rinsing with vinegar (I) compared to not rinsing with vinegar or another intervention (C) increase survival, tissue healing, functional recovery, pain, complications, time to resumption of usual activities, restoration to the pre-exposure condition and time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "jellyfish"] OR [mh Scyphozoa] OR [mh Cubozoa] OR [mh "Cnidarian venoms"] OR jellyfish:ti,ab,kw OR Scyphozoa:ti,ab,kw OR Cubozoa:ti,ab,kw OR "Cnidarian venom*":ti,ab,kw **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Scyphozoa"[Mesh] OR "Cubozoa"[Mesh] OR "Cnidarian Venoms"[Mesh] OR jellyfish[TIAB] OR Scyphozoa[TIAB] OR Cubozoa[TIAB] OR "Cnidarian Venom*"[TIAB] 2. "Acetic Acid"[Mesh] OR vinegar[TIAB] OR "acetic acid"[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'jellyfish'/exp OR 'Cubozoa'/exp OR 'jellyfish sting'/exp OR jellyfish:ab,ti OR Cubozoa:ab,ti OR Scyphozoa:ab,ti OR "Cnidarian venom":ab,ti 2. 'vinegar'/exp OR vinegar:ab,ti OR 'acetic acid':ab,ti 3. 1-2 AND
Search date	07 April 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence).

	Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Jelllyfish sting – Sting inhibitor lotion (Prevention)

Question (PICO)	In humans (P), does the use of a jellyfish sting inhibitor lotion (I) compared to not using a sting inhibitor lotion (C) effective to prevent jellyfish stings (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "jellyfish"] OR [mh Scyphozoa] OR [mh Cubozoa] OR [mh "Cnidarian venoms"] OR jellyfish:ti,ab,kw OR Scyphozoa:ti,ab,kw OR Cubozoa:ti,ab,kw OR "Cnidarian venom*":ti,ab,kw **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Scyphozoa"[Mesh] OR "Cubozoa"[Mesh] OR "Cnidarian Venoms"[Mesh] OR jellyfish[TIAB] OR Scyphozoa[TIAB] OR Cubozoa[TIAB] OR "Cnidarian Venom*"[TIAB] 2. "Accident Prevention"[Mesh] OR "Primary Prevention"[Mesh:NoExp] OR "Health Education"[Mesh] OR "Health Behavior"[Mesh] OR "Preventive Medicine"[Mesh] OR "prevention and control"[Subheading] OR prevent*[TIAB] 3. 1-2 AND

	Embase (via Embase.com interface) using the following search strategy: 1. 'jellyfish'/exp OR 'Cubozoa'/exp OR 'jellyfish sting'/exp OR jellyfish:ab,ti OR Cubozoa:ab,ti OR Scyphozoa:ab,ti OR "Cnidarian venom":ab,ti 2. 'prevention'/exp OR 'health education'/exp OR 'health behavior'/exp OR 'self examination'/de OR 'preventive medicine'/exp OR *'prevention':lnk* OR prevent*:ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	15 April 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included (but considered as indirect evidence). In case of preventive interventions: studies on primary prevention of injuries and diseases at household or community levels that describe interventions with a potential immediate effect. Studies on preventive programmes or campaigns that consist of training or provision of an information leaflet, booklet, sticker. Exclude: Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. Secondary or tertiary prevention. Interventions at policy level. Interventions based on drugs or vaccines. The following programmes: one-to-one programmes, home safety checks, free provision of materials, peer tutoring, information from medical doctors. Studies specifically intended for industrially specific situations (workplace related) **Outcome**: Include: health outcome measures (including adverse effects). Studies on the incidence of accidents. Exclude: studies on feasibility of or compliance with interventions (behavioral outcomes). Measures of knowledge or attitudes. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies. **Language**: Include: English **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Boulware, 2006, USA	Experimental: Randomized controlled trial (within subjects)	10 individuals (7 men, 3 women), mean age 29±2 years, intending to snorkel were given 26 g samples of Safe Sea SPF15 and Coppertone SPF15. These individuals participated for a total of 82 paired water exposures	1) Safe Sea sting inhibitor lotion 2) Coppertone placebo lotion Participants applied each lotion to opposite sides of their body 10 min prior to swimming. Participants swam for up to 45 minutes.	
Kimball, 2004, USA	Experimental: Randomized controlled trial	24 adult subjects were enrolled in the study. 12 subjects were exposed to *C fuscenscens* jellyfish, 12	1) Inhibitor lotion: Safe Sea 2) Conventional sunscreen: Coppertone SPF 15	

	(within subjects)	subjects were exposed to *C quadrumanus* jellyfish. Subjects were randomized to receive application of either the inhibitor lotion or the conventional sunscreen to the left arm, and the other lotion to the right arm.	Inhibitor lotion or placebo sunscreen were applied to an area of 18 x 6 cm on each forearm and allowed to dry for 10 minutes. Tentacles of jellyfish were then left in contact with the forearm for 10 and 30 seconds for *C quadrumanus* and *C fuscenscens* respectively.	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Jellyfish stings (stings/10 exposures)	Sting inhibitor lotion vs placebo	Statistically significant: 0.2±1.5 vs 1.3±3.4 RR: 0.18, 95%CI [0.04; 0.79] (p=0.02) *In favour of sting inhibitor lotion*	1, 10 vs 10 § (within subjects) = 82 paired water exposures	Boulware, 2006
Number of persons with discomfort		*C fuscenscens:* Statistically significant: 2/12 vs 12/12 §£ (p<0.01) *In favour of sting inhibitor lotion*	1, 12 vs 12 (within subjects)	Kimball, 2004
		C quadrumanus: Statistically significant: 3/12 vs 10/12 §£ (p<0.01) *In favour of sting inhibitor lotion*		
Number of persons with erythema		*C fuscenscens:* Statistically significant: 0/12 vs 12/12 §£ (p<0.01) *In favour of sting inhibitor lotion*		
		C quadrumanus: Statistically significant: 1/12 vs 9/12 §£ (p<0.01) *In favour of sting inhibitor lotion*		

Mean ± SD (unless otherwise indicated)
£ No CI available.
§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Boulware, 2006	yes, both lotions were in identical containers, but not mentioned how randomization was done	No, both lotions looked and smelled identical and were in identical containers	No	No	Within subjects
Kimball, 2006	Yes, not mentioned how randomization or blinding was done	Yes, not mentioned how blinding was done	No	No	Within subjects

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/low number of events
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is limited evidence from 2 experimental studies in favour of Sting inhibitor lotion. It was shown that sting inhibitor lotion resulted in a statistically significant decrease of number of stings, pain and erythema, compared to placebo (conventional sunscreen lotion) (Boulware 2006, Kimball 2004). Evidence is of low quality and results cannot be considered precise due to limited sample size.
Reference(s)	**Articles** Boulware DR. *A randomized, controlled field trial for the prevention of jellyfish stings with a topical sting inhibitor*. J Travel Med 2006, 13(3):166-171 Kimball AB, Arambula KZ, Stauffer AR, Levy V, Davis VW, Liu M, Rehmus WE, Lotan A, Auerbach PS. *Efficacy of a jellyfish sting inhibitor in preventing jellyfish stings in normal volunteers*. Wilderness and Environmental Medicine 2004, 15:102-108

Marine animals – Warm water (First aid)

Question (PICO)	In humans with stings from marine animals (P) is application of warm water (I) compared to not doing this (C) effective as a first aid treatment to increase tissue healing, functional recovery, pain, complications, restoration to the pre-exposure condition, time to resolution of symptoms, deactivation of the venom (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "Marine toxins"] OR [mh "Sea urchins"] OR [mh "Fishes, Poisonous"] **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Marine Toxins"[Mesh] OR "Sea Urchins"[Mesh] OR "Fishes, Poisonous"[Mesh] OR urchin [TIAB] OR hedgehog [TIAB] OR sand dollar*[TIAB] OR sand-dollar*[TIAB] OR trachinus vipera[TIAB] 2. "Hot Temperature"[Mesh] OR "Acetic Acid"[Mesh] OR vinegar[TIAB] OR "acetic acid"[TIAB] OR "hot water"[TIAB] OR "warm water"[TIAB]) 3. 1 AND 2 **Embase** (via Embase.com interface) using the following search strategy: 1. 'marine toxin'/exp OR 'sea urchin'/exp OR 'toxic fish'/exp OR urchin:ab,ti OR hedgehog:ab,ti OR (sand NEXT/1 dollar*):ti,ab OR 'trachinus vipera':ab,ti 2. 'heat'/exp OR 'acetic acid'/exp OR vinegar:ab,ti OR 'acetic acid':ab,ti OR 'hot water':ab,ti OR 'warm water':ab,ti 3. 1 AND 2 Systematic review, retrieved with the above searches, and used as source for individual studies: Atkins, 2006 Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in MEDLINE (via PubMed interface).
Search date	30 June 2015

In/Exclusion criteria	**Population**: Include: people or healthy volunteers with stings of marine animals, including a sea urchin, trachinus vipera, stingray, … **Intervention**: Include: use of warm or hot water **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Russell, 1958, United States	Experimental: non-randomized controlled trial (within subjects design)	Six healthy volunteers each received an injection of extracted, concentrated stingray venom into one finger of each hand	Hot water vs cold water immersion	placed one hand in cold, and the other in hot water

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Initial pain relief	Hot water vs cold water immersion	Not statistically significant: 6/6 vs 0/6 § RR: 13.00, 95%CI [0.89;189.39] ¥ (p=0.06) *	1, 6 vs 6 (within subjects)	Russell, 1958
Complete analgesia at 30 minutes		Not statistically significant: 5/5 vs 0/5 § RR: 11.00, 95%CI [0.77;158.01] ¥ (p=0.08) *	1, 5 vs 5 (within subjects)	

* Calculations done by the reviewer(s) using Review Manager software

§ Imprecision (limited sample size or low number of events)

¥ Imprecision (large variability of results)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Russell, 1958	Yes	Yes	No	No	Within subjects design

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes, lack of data
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion(s)	There is limited evidence neither in favour of the intervention nor the control: a statistically significant increase of pain relief, using hot water compared to cold water immersion could not be demonstrated (Russell 1958). Evidence is of low quality and results of this study are imprecise due to limited sample size and lack of data.
Reference(s)	**Articles** Russell FE, Panos TC, Kang LW, Warner AM, Colket TC. *Studies on the mechanism of death from stingray venom; a report of two fatal cases*. Am J Med Sci 1958, 235(5):566-84 **Systematic reviews** Atkinson PR, Boyle A, Hartin D, McAuley D. *Is hot water immersion an effective treatment for marine envenomation?* Emerg Med J 2006, 23(7):503-8

Marine animals – Sting removal (First aid)

Question (PICO)	In humans with stings from marine animals (P) is removal of the sting(s) (I) compared to not doing this (C) effective as a first aid treatment to increase tissue healing, functional recovery, pain, complications, restoration to the pre-exposure condition, time to resolution of symptoms, deactivation of the venom (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "Marine toxins"] OR [mh "Sea urchins"] OR [mh "Fishes, Poisonous"] **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Marine Toxins"[Mesh] OR "Sea Urchins"[Mesh] OR "Fishes, Poisonous"[Mesh] OR urchin [TIAB] OR hedgehog [TIAB] OR sand dollar*[TIAB] OR sand-dollar*[TIAB] OR trachinus vipera[TIAB] 2. remov*[TIAB] OR extract*[TIAB] 3. Sting*[TIAB] OR tentacle*[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'marine toxin'/exp OR 'sea urchin'/exp OR 'toxic fish'/exp OR urchin:ab,ti OR hedgehog:ab,ti OR (sand NEXT/1 dollar*):ti,ab OR 'trachinus vipera':ab,ti 2. sting*:ab,ti OR tentacle*:ab,ti 3. remov*:ab,ti OR extract*:ab,ti 4. 1-3 AND
Search date	30 June 2015
In/Exclusion criteria	**Population**: Include: people or healthy volunteers with stings of marine animals, including a sea urchin, trachinus vipera,… **Intervention**: Include: removal of sting or tentacles **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers.

	Design: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion(s)	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Marine animals – Vinegar (First aid)

Question (PICO)	In humans with stings from marine animals (P) is application of vinegar (I) compared to not doing this (C) effective as a first aid treatment to increase tissue healing, functional recovery, pain, complications, restoration to the pre-exposure condition, time to resolution of symptoms, deactivation of the venom (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "Marine toxins"] OR [mh "Sea urchins"] OR [mh "Fishes, Poisonous"] **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Marine Toxins"[Mesh] OR "Sea Urchins"[Mesh] OR "Fishes, Poisonous"[Mesh] OR urchin [TIAB] OR hedgehog [TIAB] OR sand dollar*[TIAB] OR sand-dollar*[TIAB] OR trachinus vipera[TIAB] 2. "Hot Temperature"[Mesh] OR "Acetic Acid"[Mesh] OR vinegar[TIAB] OR "acetic acid"[TIAB] OR "hot water"[TIAB] OR "warm water"[TIAB]) 3. 1 AND 2 **Embase** (via Embase.com interface) using the following search strategy: 1. 'marine toxin'/exp OR 'sea urchin'/exp OR 'toxic fish'/exp OR urchin:ab,ti OR hedgehog:ab,ti OR (sand NEXT/1 dollar*):ab,ti OR 'trachinus vipera':ab,ti 2. 'heat'/exp OR 'acetic acid'/exp OR vinegar:ab,ti OR 'acetic acid':ab,ti OR 'hot water':ab,ti OR 'warm water':ab,ti 3. 1 AND 2
Search date	30 June 2015
In/Exclusion criteria	**Population**: Include: people or healthy volunteers with stings of marine animals, including a sea urchin, trachinus vipera, stingray, …

	Intervention: Include: use of vinegar **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion(s)	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

POISONING

Poisoning – Left decubitus body position (First Aid)

Question (PICO)	In victims who have been poisoned (P) is lying the victim on his left side (I) compared to not doing this (C) effective to slowing down spreading of the poison (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "posture"] OR posture:ti,ab,kw OR (left NEXT side):ti,ab,kw OR (body NEXT position):ti,ab,kw 2. [mh "poisoning"] OR poisoning:ti,ab,kw OR (toxic NEXT ingestion):ti,ab,kw OR (toxic NEXT ingestions):ti,ab,kw OR intoxication:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for systematic reviews, experimental and observational studies using the following search strategy: 1. "left side"[TIAB] OR "body position"[TIAB] OR "posture"[Mesh] OR "posture"[TIAB] 2. "poisoning"[Mesh] OR "poisoning"[TIAB] OR "toxic ingestion"[TIAB] OR "toxic ingestions"[TIAB] OR "intoxication"[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) for systematic reviews, experimental and observational studies using the following search strategy: 1. 1.'body posture'/exp OR 'left side':ab:ti OR 'body position':ab:ti OR 'body posture':ab:ti 2. 2.'intoxication'/exp OR 'poisoning':ab:ti OR 'toxic ingestion':ab:ti OR 'toxic ingestions':ab:ti OR 'intoxication':ab:ti 3. 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	13 February 2015
In/Exclusion criteria	**General project-related eligibility criteria:** **Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available.

	An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies. **Topic-related study eligibility criteria:** **Intervention:** exclude: ingestion of food or drinks as measure for the ingestion of poison

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Vance, 1992, USA	Experimental: randomised controlled trial (within subjects design)	Six male and six female healthy, adult volunteer subjects with no concurrent drug use or medications affecting gastrointestinal function. All subjects are highly conditioned firefighters. To simulate an acute overdose, fasted subjects ingested 80 mg/kg acetaminophen in the form of 160-mg paediatric tablets.	Left lateral decubitus position vs right lateral decubitus. The different positions were performed by all subjects in random order with a three-day washout phase between trials.	Each subject then remained in the body position for that trial for two hours. Acetaminophen levels were obtained at IS-minute intervals, and a two-hour area under the curve (AUC) was calculated for each subject trial to represent total drug absorption during each study period. Acetaminophen is not known to induce gastric emptying changes.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
80 mg/kg acetaminophen uptake (AUC, mg/l/min)	Left lateral decubitus position vs right lateral decubitus	Statistically significant: 6,006 ± 2,614 vs 8,950 ± 1,405 MD: -2,94* ($p<0.05$) *in favour of left lateral decubitus position*	1, 12 vs 12 (within subjects design) §	Vance, 1992

* Calculations done by the reviewer(s) using Review Manager software
§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Vance, 1992	Unclear, mode of allocation concealment not described (but randomisation was performed)	No, investigators were blinded to all results until all trials were completed	No	No	Within subjects design

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	Although the study is a cross-over design, the pharmacokinetics of Acetaminophen are well known and are used as basis to determine the time lapse between two body positions.
Imprecision	-1	Limited sample size
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Moderate [B]**	

Conclusion	There is limited evidence in favour of the left decubitus position: It was shown that the left decubitus position resulted in a statistically significant decrease of acetaminophen uptake (measure of gastric empting), compared to the right decubitus position (Vance 1996). Evidence is of moderate quality and results cannot be considered precise due to limited sample size.
Reference(s)	**Articles** Vance MV, Selden BS, Clark RF. *Optimal patient position for transport and initial management of toxic ingestions.* Annals of Emergency Medicine 1992, 21(3):243-246.

Poisoning – Activated charcoal (First Aid)

Question (PICO)	In victims who have been poisoned (P) is taking activated charcoal (I) compared to not doing this (C) effective to change functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. (active NEXT administration):ti,ab,kw OR (activated NEXT charcoal):ti,ab,kw 2. [mh "poisoning"] OR poisoning:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for systematic reviews, experimental and observational studies using the following search strategy: 1 "active charcoal"[TIAB] OR "activated charcoal"[TIAB] 2. "poisoning"[Mesh] OR "poisoning"[TIAB] 3. "Self Administration"[Mesh] OR "Self Medication"[Mesh] OR "Home Nursing"[Mesh] OR "First Aid"[Mesh] OR "pre-hospital"[TIAB] OR "prehospital"[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) for systematic reviews, experimental and observational studies using the following search strategy: 1.'activated carbon'/exp OR 'active carbon':ab:ti OR 'activated carbon':ab:ti 2. 'intoxication'/exp OR 'poisoning':ab:ti OR 'intoxication':ab:ti 3. 'drug self administration'/exp OR 'self medication'/exp OR 'home care'/exp OR 'first aid'/exp OR 'emergency care'/exp 3. 1-3 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in MEDLINE (via PubMed interface).

Search date	17 March 2015
In/Exclusion criteria	**General project-related eligibility criteria:** **Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies. **Topic-related study eligibility criteria:** **Intervention:** Include: medicine intake (instead of poison), independent of its dose (i.e. therapeutic dose, supra-therapeutic dose, etc.) Exclude: charcoal hemoperfusion; active charcoal included in an entire detoxification protocol consisting of for example gastric lavage, charcoal hemoperfusion, and cyclophosphamide and steroid pulse therapies; activated charcoal mixed with cathartics for gastric decontamination; multiple charcoal dose; simultaneous poison and charcoal ingestion.

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Kivistö, 1991, Finland	Experimental: non-randomized controlled trial	12 healthy subjects who take 400 mg amiodarone. Their health was based on medical history, electrocardiogram and the results of routine laboratory tests (intervention group: 6 subjects, 23 ± 1 years, 67 ± 5.1 kg; control group: 6 subjects, 23 ± 1 years, 68 ± 4.6 kg) (Data presented as mean ± standard error of the mean)	by 25 g charcoal ingestion (after 1.5 h) vs no charcoal ingestion	Amiodarone is an anti-arrhythmic drug Charcoal suspension was prepared by pouring tap water into a plastic bottle containing charcoal powder and shaking the mixture for 1 minute.
Merigian, 2002, VSA	Experimental: randomized controlled trial	1479 adult patients presenting to the emergency department with diagnose of self-poisoning Drug(s): Forty-eight percent of all study patients reported ingesting a single agent; 52% reported ingesting two	50 mg charcoal and/or supportive therapy when necessary vs supportive therapy when	All patients received supportive therapy when necessary. Such therapy included, but was not limited to, maintenance of

		or more drugs. Central nervous system (CNS) depressants were the most common class of drug ingested in this patient population. Drugs included in this classification were benzodiazepines, barbiturates, opioids, antiseizure medication(s), antidepressants, and major and minor tranquilizers.	necessary without charcoal	airway, pulmonary hygiene, intubation, circulatory support, and assurance of adequate urine output and renal function. Psychiatric evaluation followed medical clearance in all cases of intentional overdose.
Olkkola, 1984, Finland	Experimental: randomized controlled trial (within subjects design)	6 healthy female volunteers who take 1 or 5 g aminosalicylic acid. Their health was based on physical examination and routine laboratory tests (age 22-36, body weight: 54-65 kg)	50 g charcoal ingestion vs no charcoal ingestion	Within subjects design: 2 weeks interval
Wannakul, 2010, Thailand	Experimental: randomized controlled trial (within subjects design)	12 male volunteers	50 g charcoal ingestion after 0.25 hour vs no charcoal ingestion	Within subjects design: with 1 week interval

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Drug bioavailability (measured in blood)	Activated charcoal vs no activated charcoal	Statistically significant: Reduction with 50% in intervention group Effect size and CI cannot be calculated † (p<0.05) *in favour of charcoal ingestion*	1, 6 vs 6 §	Kivistö, 1991
		1g aminosalicylic acid: Statistically significant: Reduction with 95% in intervention group Effect size and CI cannot be calculated † (p<0.05) *in favour of charcoal ingestion*	1, 6 vs 6 (within subjects design) §	Olkkola, 1984
		5 g aminosalicylic acid: Statistically significant: Reduction with 90% in intervention group Effect size and CI cannot be calculated † (p<0.05) *in favour of charcoal ingestion*		
		Statistically significant: Reduction with 40.9% in intervention group Effect size and CI cannot be calculated † (p=0.01) *in favour of charcoal ingestion*	1, 12 vs 12 (within subjects design) §	Wannakul, 2010
Complications: vomiting		Statistically significant: 23% vs 13% Effect size and CI cannot be calculated † *(p<0.01) against charcoal ingestion i.e. individuals who have taken charcoal vomited more than the control group*	1, 1479 (the number of participants in each study group was not described)	Merigian, 2002

† Imprecision (lack of data)

§ Imprecision (limited sample size or low number of events)

Quality of evidence:

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Kivistö, 1991	Unclear, not specified in the article	Unclear, not specified in the article	No	No	Randomisation was not performed, although the baseline characteristics were very similar in all groups
Merigian, 2002	Unclear, not specified in the article	Unclear, not specified in the article	Unclear, not specified in the article	Yes	Randomisation according to even-odd protocol
Olkkola, 1984	Unclear, not specified in the article	Unclear, not specified in the article	No	Yes, the study protocol is not clear for drug amounts > 5g. Therefore, only results of 1 and 5 g were reported in the evidence summary	Within subjects design
Wannakul, 2010	Unclear, not specified in the article	Unclear, not specified in the article	No	No	Within subjects design

Level of evidence

Drug availability

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes in studies that investigate drug bioavailability; Lack of data
Inconsistency	0	
Indirectness	-1	Drug <-> poison
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Complications

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	
Imprecision	-1	Lack of data
Inconsistency	0	
Indirectness	-1	Drug <-> poison
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Conclusion	There is limited evidence in favour of activated charcoal ingestion after poisoning: It was shown that activated charcoal resulted in a statistically significant reduction in drug viability, compared to no activated charcoal (Kivistö 1991, Olkkola 1984, Wannakul 2010). Evidence is of very low quality and results cannot be considered precise due to limited sample size and lack of data. It was also shown that activated charcoal resulted in a statistically significant increase in complications such as vomiting, compared to no activated charcoal (Merigian 2002). Evidence is of very low quality and results cannot be considered precise due to lack of data.
Reference(s)	**Articles**

	Kivistö KT, Neuvonen PJ. *Effect of activated charcoal on the absorption of amiodarone.* Hum Exp Toxicol 1991, 10(5):327-329. Merigian KS, Blaho KE. *Single-dose oral activated charcoal in the treatment of the self-poisoned patient: a prospective, randomized, controlled trial.* Am J Ther 2002, 9(4):301-308. Olkkola KT. *Effect of charcoal-drug ratio on antidotal efficacy of oral activated charcoal in man*. Br J Clin Pharmacol 1985, 19(6):767-773. Wananukul W, Klaikleun S, Sriapha C, Tongpoo A. *Effect of activated charcoal in reducing paracetamol absorption at a supra-therapeutic dose.* J Med Assoc Thai 2010, 93(10):1145-1149.

Poisoning – Drinking milk (First Aid)

Question (PICO)	In humans with poisoning (P), is drinking milk (I) compared to not doing this (C) effective to change functional recovery, complications, time to resumption of usual activities, restoration to the pre-exposure condition, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Poisoning"] OR poison*:ti,ab OR intoxication:ti,ab 2. [mh "milk"] OR milk:ti,ab 3. 1 AND 2 **MEDLINE** (via PubMed interface) using the following search strategy: 7. "Poisoning"[Mesh] OR poison*[TIAB] OR intoxication[TIAB] 8. "Drinking"[Mesh] OR drink*[TIAB] 9. "Milk"[Mesh] OR milk[TIAB] 10. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 7. 'intoxication'/exp OR poison*:ab,ti OR intoxication:ab,ti 8. 'drinking'/exp OR drink*:ab,ti 9. 'milk'/exp OR milk:ab,ti 10. 1-3 AND
Search date	7 September 2015
In/Exclusion criteria	**Population**: Include: people who have been poisoned **Intervention**: Include: drinking milk or water **Outcome**: Include: absorption of poison, functional recovery, complications, time to resumption of usual activities, restoration to the pre-exposure condition, time to resolution of symptoms **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion(s)	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Poisoning – Drinking water (First Aid)

Question (PICO)	PICO: In people that are poisoned (P), does giving the poisoned person water (I), compared to not giving the poisoned person water (C), influence survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of the symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "poisoning"] OR [mh "poisons"] OR poison*:ti,ab,kw OR intoxica*:ti,ab,kw 2. [mh "drinking water"] OR [mh "water"] OR water:ti,ab,kw 3. [mh "drinking"] OR drinking:ti,ab,kw OR intake:ti,ab,kw OR consum*:ti,ab,kw OR ingest*:ti,ab,kw 4. 1-3 AND **MEDLINE** (via PubMed interface) for guidelines and systematic reviews using the following search strategy: 1. "poisoning"[MeSH] OR "poisons"[MeSH] OR poison*[TIAB] OR intoxica*[TIAB] 2. "drinking water"[MeSH] OR "water"[MeSH] OR water[TIAB] 3. "drinking"[MeSH] OR drinking[TIAB] OR intake[TIAB] OR consum*[TIAB] OR ingest*[TIAB] 4. "First Aid"[Mesh] OR "Community Health Workers"[Mesh] OR "Emergency Treatment"[Mesh:NoExp] OR "Emergency Medical Services"[Mesh:NoExp] OR "Emergency Service, Hospital"[Mesh] OR "Poison Control Centers"[Mesh] OR "Transportation of Patients"[Mesh] OR "Primary Health Care"[Mesh:NoExp] OR "Acute disease"[Mesh] OR "emergencies" [Mesh] OR "self care"[Mesh] OR "acute management" [TIAB] OR "immediate care" [TIAB] OR "prehospital treatment" [TIAB] 5. 1-4 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'intoxication'/exp OR 'poison'/exp OR poison*:ab,ti OR intoxica*:ab,ti 2. 'drinking water'/exp OR 'water'/exp OR water:ab,ti 3. 'drinking'/exp OR drinking:ab,ti OR intake:ab,ti OR consum*:ab,ti OR ingest*:ab,ti 4. 'emergency treatment'/de OR 'first aid'/exp OR 'health auxiliary'/exp OR 'emergency care'/de OR 'emergency health service'/exp OR 'poison center'/exp OR 'ambulance'/exp OR 'patient transport'/exp OR 'primary health care'/de OR 'acute disease'/exp OR 'emergency'/exp OR 'self care'/exp OR (acute NEXT/1 manag*):ab,ti OR (prehospital NEXT/1 treat*):ab,ti 5. 1-4 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in MEDLINE (via PubMed interface).

Search date	10th May 2016
In/Exclusion criteria	**Population:** Include: People that are poisoned. Healthy volunteers receiving a non-poisonous drug. **Intervention:** Include: Drinking water. Exclude: Any other form of first aid management. **Comparison:** Include: Other first aid management, no first aid management. **Outcome:** Include: effectiveness and feasibility of drinking water for survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of the symptoms and other health outcomes (including adverse events). **Study design:** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: observational studies if intervention is already included in experimental studies, case series, cross-sectional studies, animal studies, ex vivo or in vitro studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English, French, German, Dutch. **Publication year**: Include: all years.

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison/Risk factor	Remarks
Lapatto-Reiniluoto, 1999, Finland	Experimental: Randomised controlled trial (within subjects design)	9 healthy volunteers, 2 male and 7 female, aged 19-40 years, ingesting 3 tablets, consisting of 5 mg diazepam, 400 mg ibuprofen and 20 mg citalopram	Group 1: 200 ml water, 30 min after ingestion Group 2: 25 g activated charcoal (AC) in a 200 mL suspension, 30 min after ingestion Group 3: Gastric lavage, followed by 25 g AC in a 200 mL suspension, 30 min after lavage [Only comparison Group 1 vs Group 2 was extracted, as AC is considered the gold standard]	The study had 80% power to detect a 30% difference in AUC at the 0.05 level
Lapatto-Reiniluoto, 2000a, Finland	Experimental: Randomised controlled trial (within subjects design)	9 healthy volunteers, 4 male and 5 female, aged 19-33 years, ingesting 2 tablets and 1 capsule, consisting of 150 mg moclobemide, 10 mg temazepam and 80 mg verapamil	Group 1: 200 mL water, 5 min after ingestion Group 2: 25 g AC in a 200 ml water suspension, 5 min after ingestion Group 3: gastric lavage, 5 min after ingestion [Only comparison Group 1 vs Group 2 was extracted, as AC is considered the gold standard]	

Lapatto-Reiniluoto, 2000b, Finland	Experimental: Randomised controlled trial (within subjects design)	9 healthy volunteers, 5 male and 4 female, ingesting 2 tablets and 1 capsule, consisting of 150 mg moclobemide, 10 mg temazepam and 80 mg verapamil	Group 1: 200 mL water, 30 min after ingestion Group 2: 25 g AC in a 200 ml water suspension, 30 min after ingestion Group 3: gastric lavage, 30 min after ingestion [Only comparison Group 1 vs Group 2 was extracted, as AC is considered the gold standard]	
Lapatto-Reiniluoto, 2001, Finland	Experimental: Randomised controlled trial (within subjects design)	9 healthy volunteers, 4 male and 5 female, aged 20-39 years, ingesting 3 tablets, consisting of 200 mg theophylline, 120 mg verapamil and 200 mg carbamazepine	Group 1: 200 mL water, 60 min after ingestion Group 2: 25 g AC in a 200 ml water suspension, 60 min after ingestion Group 3: 25 g AC in a 200 ml water suspension, 60 min after ingestion, followed by whole bowel irrigation	
Neuvonen, 1980, Finland	Experimental: Randomised controlled trial (within subjects design)	5 healthy female volunteers, aged 21-46 years, ingesting 100 mg dapsone for 5 days	Group 1: 300 mL water, 10 h after the last dapsone ingestion Group 2: 25 g AC in a 300 mL suspension, 10 h after the last dapsone ingestion, followed by 4 doses of 17 g AC at 12 h intervals	Dapsone is a drug with a long t ½, enterohepatic cycle and is being transformed to monoacetyldapsone
Neuvonen, 1983a, Finland	Experimental: Randomised controlled trial (within subjects design)	6 healthy volunteers, aged 27-40 years, ingesting 4 tablets, consisting of 1000 mg paracetamol, 500 mg tetracycline and 350 mg aminophylline with 100 mL water	Group 1: 300 mL water, 5 min after ingestion Group 2: 50 g AC in a 300 mL suspension, 5 min or 30 min after ingestion Group 3: 20 mL syrup of ipecac and 300 mL water, 5 min or 30 min after ingestion [Only comparison Group 1 vs Group 2 after 5 min was extracted, as AC is considered the gold standard]	Data from urinary excretion of tetracycline was not extracted, as these data were not available for the other drugs
Neuvonen, 1983b, Finland	Experimental: Randomised controlled trial (within subjects design)	6 healthy volunteers, one male and 5 female, aged 19-49 years, ingesting 2 tablets, consisting of 500 mg tolbutamide and 300 mg sodium valproate with 50 ml water	Group 1: 400 mL water, 5 min after ingestion Group 2: 50 g AC in a 400 mL suspension, 5 min after ingestion	
Neuvonen, 1984, Finland	Experimental: Randomised controlled trial	6 healthy volunteers, aged 19-23 years, 4 males and 2 females, ingesting 4 tablets	Group 1: 300 mL water, 5 min after ingestion	

	(within subjects design)	and 1 capsule, consisting of 200 mg disopyramide, 50 mg indomethacin and 200 mg trimethoprim with 300 mL water	Group 2: 2.5 g AC Norit A® in a 300 mL suspension, 5 min after ingestion Group 3: 5 g AC Norit A® in a 300 mL suspension, 5 min after ingestion Group 4: 10 g AC Norit A® in a 300 mL suspension, 5 min after ingestion Group 5: 50 g AC Norit A® in a 300 mL suspension, 5 min after ingestion Group 6: 10 g AC PX-21® in a 300 mL suspension, 5 min after ingestion [Only comparison Group 1 vs Group 2 was extracted, as this is the most conservative dose of AC used]	
Neuvonen, 1988	Experimental: Randomised controlled trial (within subjects design)	6 healthy volunteers, four males and 2 females, aged 22-35 years, ingesting 3 tablets, consisting of 0.25 mg digoxin, 400 mg carbamazepine and 40 mg furosemide	Group 1: 300 mL water, 5 min after ingestion Group 2: 10 g colestipol hydrochloride in a suspension of 150 mL water, followed by 150 mL water, 5 min after ingestion Group 3: 8 g cholestyramine anhydrous in a suspension of 150 mL water, followed by 150 mL water, 5 min after ingestion Group 4: 8 g AC in a suspension of 150 mL, followed by 150 mL water, 5 min after ingestion [Only comparison Group 1 vs Group 4 was extracted, as AC is considered the gold standard]	
Olkkola, 1984, Finland	Experimental: Randomised controlled trial (within subjects design)	6 healthy volunteers, 1 male and 5 females, aged 21-26 years, ingesting 3 capsules and 2 tablets, consisting of 1000 mg aspirin, 200 mg mexiletine hydrochloride and 400 mg tolfenamic acid with 100 mL water	Group 1: 150 mL water, 5 min after ingestion Group 2: 25 g AC in a suspension of 150 mL water, 5 min after ingestion Group 3: 25 g AC in a suspension of 150 mL water, 60 min after ingestion Group 4: a standardized meal, consisting of 150 g meat balls and a roll with cheese before ingestion and 150 mL water, 5 min after ingestion	

			Group 5: a standardized meal, consisting of 150 g meat balls and a roll with cheese before ingestion and 25 g AC in a suspension of 150 mL water, 5 min after ingestion Group 6: a standardized meal, consisting of 150 g meat balls and a roll with cheese before ingestion and 25 g AC in a suspension of 150 mL water, 60 min after ingestion [Only comparison Group 1 vs Group 2, as AC is considered the gold standard]	
Wananukul, 2010, Thailand	Experimental: Randomised controlled trial (within subjects design)	12 healthy male volunteers, ingesting 60 mg/kg paracetamol	Group 1: 500 mL water, 15 min after ingestion Group 2: 50 g AC in a suspension of 500 mL water, 15 min after ingestion	

Synthesis of findings

Outcome	Comparison/Risk factor	Effect Size	#studies, # participants	Reference
5 min after drug intake				
Peak plasma moclobemide concentration (ng/mL)	Water vs AC	Statistically significant: 1110±417 vs 5.9±8.2 MD: 1104.1 £† (p<0.01) *In favour of AC*	1, 9 vs 9 § (within subjects design)	Lapatto-Reiniluoto, 2000a
Plasma moclobemide concentration (AUC, ng/mL*h)		Statistically significant: 5050±3230 vs 13.5±19.2 MD: 5036.5 £† (p<0.01) *In favour of AC*		
24h moclobemide urinary excretion (µg)		Statistically significant: 1300±822 vs 2.3±3.2 MD: 1297.7 £† (p<0.05) *In favour of AC*		
Peak plasma temazepam concentration (ng/mL)		Statistically significant: 421±120 vs 21.9±35.2 MD: 399.1 £† (p<0.01) *In favour of AC*		
Plasma temazepam concentration (AUC, ng/mL*h)		Statistically significant: 2280±1030 vs 108±117 MD: 2172 £† (p<0.01) *In favour of AC*		

24h temazepam urinary excretion (µg)		Statistically significant: 21±14 vs 6.0±6.2 MD: 15 £† (p<0.05) *In favour of AC*		
Peak plasma verapamil concentration (ng/mL)		Statistically significant: 38.6±20.9 vs 2.3±2.6 MD: 36.3 £† (p<0.01) *In favour of AC*		
Plasma verapamil concentration (AUC, ng/mL*h)		Statistically significant: 223±118 vs 16.2±13.4 MD: 206.8 £† (p<0.01) *In favour of AC*		
24h verapamil urinary excretion (µg)		Statistically significant: 518±311 vs 30±48 MD: 488 £† (p<0.01) *In favour of AC*		
Peak serum paracetamol concentration (mg/L)		Statistically significant: 14.9±4.9 vs 2.6±0.45 MD: 12.3 £† (p<0.01) *In favour of AC*	1, 6 vs 6 § (within subjects design)	Neuvonen, 1983a
Peak serum tetracycline concentration (mg/L)		Statistically significant: 3.3±0.98 vs 0.10±0.10 MD: 3.2 £† (p<0.01) *In favour of AC*		
Peak serum aminophylline concentration (mg/L)		Statistically significant: 4.0±1.47 vs 1.2±0.49 MD: 2.8 £† (p<0.01) *In favour of AC*		
Peak serum tolbutamide concentration (mg/L)		Statistically significant: 52.6±8.3 vs 4.7±1.1 MD: 47.9 £† (p<0.001) *In favour of AC*		Neuvonen, 1983b
Serum tolbutamide concentration (AUC, mg/h*L)		Statistically significant: 714±130 vs 609±159 MD: 104 £† (p<0.001) *In favour of AC*		
Peak serum valproate concentration (mg/L)		Statistically significant: 38.1±7.8 vs 13.6±10.1 MD: 24.5 £† (p<0.01) *In favour of AC*		
Serum valproate concentration (AUC, mg/h*L)		Statistically significant: 609±174 vs 222±130 MD: 387 £† (p<0.01) *In favour of AC*		

Peak serum disopyramide concentration (mg/L)		Not statistically significant: 3.43±1.59 vs 1.63±0.64 MD: 1.8 £† (p>0.05)		Neuvonen, 1984
Serum disopyramide concentration (AUC, mg/h*L)		Statistically significant: 38.8±19.1 vs 15.9±8.57 MD: 22.9 £† (p<0.05) *In favour of AC*		
72h disopyramide urinary excretion (mg)		Statistically significant: 132.2±25.47 vs 34.0±9.80 MD: 98.2 £† (p<0.05) *In favour of AC*		
Peak serum indomethacin concentration (mg/L)		Statistically significant: 1.89±0.76 vs 1.01±0.54 MD: 0.88 £† (p<0.05) *In favour of AC*		
Serum indomethacin concentration (AUC, mg/h*L)		Statistically significant: 8.90±3.67 vs 3.10±1.47 MD: 5.8 £† (p<0.05) *In favour of AC*		
72h indomethacin urinary excretion (mg)		Statistically significant: 2.21±0.66 vs 0.75±0.29 MD: 1.46 £† (p<0.05) *In favour of AC*		
Peak serum trimethoprim concentration (mg/L)		Statistically significant: 2.50±0.91 vs 0.19±0.12 MD: 2.31 £† (p<0.05) *In favour of AC*		
Serum trimethoprim concentration (AUC, mg/h*L)		Statistically significant: 41.50±17.88 vs 3.8±2.2 MD: 37.7 £† (p<0.05) *In favour of AC*		
72h trimethoprim urinary excretion (mg)		Statistically significant: 108.20±30.86 vs 17.40±7.35 MD: 90.8 £† (p<0.05) *In favour of AC*		
Peak plasma digoxin concentration (µg/L)		Statistically significant: 1.1±2.0 vs 0.02±0.008 MD: 1.08 £† (p<0.05) *In favour of AC*		Neuvonen, 1988
Plasma digoxin concentration (AUC, µg/L*h)		Statistically significant: 14.3±3.2 vs 0.2±0.2 MD:14.1 £† (p<0.05) *In favour of AC*		
72 h digoxin urinary excretion (µg)		Statistically significant: 87.3±12.3 vs 3.9±1.3 MD: 83.4 £†		

		(p<0.05) *In favour of AC*		
Peak plasma carbamazepine concentration (mg/L)		Statistically significant: 2.7±0.3 vs 0.28±0.18 MD: 2.42 £† (p<0.05) *In favour of AC*		
Plasma carbamazepine concentration (AUC, mg/L*h)		Statistically significant: 145±9 vs 11±11 MD: 134 £† (p<0.05) *In favour of AC*		
Peak plasma furosemide concentration (mg/L)		Statistically significant: 1.2±0.6 vs 0.01±0.008 MD: 1.19 £† (p<0.05) *In favour of AC*		
Plasma furosemide concentration (mg/L*h)		Statistically significant: 3.5±1.4 vs 0.03±0.04 MD: 3.47 £† (p<0.05) *In favour of AC*		
72 h furosemide urinary excretion (mg)		Statistically significant: 15.4±3.2 vs 0.07±0.04 MD: 15.33 £† (p<0.05) *In favour of AC*		
Peak serum aspirin concentration (mg/L)		Statistically significant: 88±14.5 vs 20.3±5.1 MD: 67.7 £† (p<0.05) *In favour of AC*	1, 9 vs 9 § (within subjects design)	Olkkola, 1984
Serum aspirin concentration (AUC, mg/L*h)		Statistically significant: 940±181 vs 218±71 MD: 722 £† (p<0.05) *In favour of AC*		
48 h aspirin urinary excretion (mg)		Statistically significant: 308±26 vs 144±12 MD:164 £† (p<0.05) *In favour of AC*		
Peak serum mexiletine concentration (mg/L)		Statistically significant: 0.3±0.05 vs 0.02±0.02 MD: 0.28 £† (p<0.05) *In favour of AC*		
Serum mexiletine concentration (AUC, mg/L*h)		Statistically significant: 2.82±0.91 vs 0.1±0.1 MD: 2.72 £† (p<0.05) *In favour of AC*		
48 h mexiletine urinary excretion (mg)		Statistically significant: 24±13.22 vs 0.79±1.27 MD: 23.21 £† (p<0.05) *In favour of AC*		

Peak serum tolfenamic acid concentration (mg/L)		Statistically significant: 3.18±1.37 vs 0.65±0.22 MD: 2.53 £† (p<0.05) *In favour of AC*		
Serum tolfenamic acid concentration (AUC, mg/L*h)		Statistically significant: 18.6±5.6 vs 2.29±0.64 MD: 16.31 £† (p<0.05) *In favour of AC*		
15 min after drug intake				
Peak plasma paracetamol concentration (mg/L)	Water vs AC	Not statistically significant: 71 vs 48.7 (median) Median difference: 22.3 £† (p>0.05)	1, 12 vs 12 § (within subjects design)	Wananukul, 2010
Plasma paracetamol concentration (AUC, mg/h*L)		Statistically significant: 313.7±29.8 vs 184.8±91.6 MD: 283.9 £† (p=0.01) *In favour of AC*		
30 min after drug intake				
Peak plasma diazepam concentration (ng/mL)	Water vs AC	Not statistically significant: 153±26.1 vs 126±47.9 MD: 27 £† (p>0.05)	1, 9 vs 9 (within subjects design)	Lapatto-Reiniluoto, 1999
Plasma diazepam concentration (AUC, ng/mL*h)		Statistically significant: 693±80.9 vs 503±160 MD: 190 £† (p<0.05) *In favour of AC*		
Peak plasma ibuprofen concentration (µg/mL)		Not statistically significant: 34.7±6.4 vs 27.3±10.9 MD: 7.4 £† (p>0.05)		
Plasma ibuprofen concentration (AUC, µg/mL*h)		Statistically significant: 119±38.3 vs 82.7±30.1 MD: 36.3 £† (p<0.05) *In favour of AC*		
Peak plasma citalopram concentration (ng/mL)		Statistically significant: 17.9±4.9 vs 8.6±5.9 MD: 9.3 £† (p<0.05) *In favour of AC*		
Plasma citalopram concentration (AUC, ng/mL*h)		Statistically significant: 131±32.9 vs 63.6±42.6 MD: 67.4 £† (p<0.05) *In favour of AC*		
Peak plasma moclobemide concentration (ng/mL)		Not statistically significant: 1291±610 vs 777±567 MD: 514 £† (p>0.05)	1, 9 vs 9 § (within subjects design)	Lapatto-Reiniluoto, 2000b
Plasma moclobemide		Statistically significant: 5284±3151 vs 2362±2021 MD: 2922 £†		

concentration (AUC, ng/mL*h)		(p<0.05) *In favour of AC*		
Peak plasma temazepam concentration (ng/mL)		Statistically significant: 445±122 vs 314±97.7 MD: 131 £† (p<0.05) *In favour of AC*		
Plasma temazepam concentration (AUC, ng/mL*h)		Statistically significant: 2460±1204 vs 1359±428 MD: 1101 £† (p<0.05) *In favour of AC*		
Peak plasma verapamil concentration (ng/mL)		Not statistically significant: 38.6±21.2 vs 32.5±28 MD: 6.1 £† (p>0.05)		
Plasma verapamil concentration (AUC, ng/mL*h)		Not statistically significant: 212±92.5 vs 143±121 MD: 69 £† (p>0.05)		
60 min after drug intake				
Peak plasma carbamazepine concentration (ng/mL)	Water vs AC	Statistically significant: 1505±260 vs 566±281 MD: 939 £† (p<0.001) *In favour of AC*	1, 9 vs 9 § (within subjects design)	Lapatto-Reiniluoto, 2001
Plasma carbamazepine concentration (AUC, ng/mL*h)		Statistically significant: 28890±5311 vs 11070±5856 MD: 17820 £† (p<0.001) *In favour of AC*		
Peak plasma theophylline concentration (ng/mL)		Statistically significant: 3038±978 vs 1028±708 MD: 2010 £† (p<0.001) *In favour of AC*		
Plasma theophylline concentration (AUC, ng/mL*h)		Statistically significant: 50130±16316 vs 12630±12078 MD: 37500 £† (p<0.001) *In favour of AC*		
Peak plasma verapamil concentration (ng/mL)		Statistically significant: 42±18 vs 18±21 MD: 24 £† (p<0.01) *In favour of AC*		
Plasma verapamil concentration (AUC, ng/mL*h)		Statistically significant: 401±141 vs 149±148 MD: 252 £† (p<0.001) *In favour of AC*		
10 h after drug intake				
Serum dapsone t½ (h)	Water vs AC	Statistically significant: 20.5±4.5 vs 10.8±0.9 MD: 9.2 £†	1, 5 vs 5 § (within subjects design)	Neuvonen, 1980

		(p<0.01) *In favour of AC*		
Serum monoacetyldapsone t½ (h)		Statistically significant: 19.3±2.7 vs 9.5±1.6 MD: 9.8 £† (p<0.01) *In favour of AC*		
96 h urinary dapsone excretion (g)		Statistically significant: 16.6±2.5 vs 6.3±2.0 MD: 10.3 £† (p<0.05) *In favour of AC*		
96 h urinary monoacetyldapsone excretion (g)		Statistically significant: 9.9±1.1 vs 4.2±2.7 MD: 5.7 £† (p<0.05) *In favour of AC*		

Mean ± SD (unless otherwise indicated)
£ CI cannot be calculated
† Imprecision (lack of data)
§ Imprecision (limited sample size)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Lapatto-Reiniluoto, 1999	Unclear, no statement was made about allocation and randomization procedure	Yes, blinding impossible by the nature of the procedures	No, all subjects were accounted for	No	Yes, study in healthy volunteers
Lapatto-Reiniluoto, 2000a	Unclear, no statement was made about allocation and randomization procedure	Yes, blinding impossible by the nature of the procedures	No, all subjects were accounted for	No	Yes, study in healthy volunteers
Lapatto-Reiniluoto, 2000b	Unclear, no statement was made about allocation and randomization procedure	Yes, blinding impossible by the nature of the procedures	No, all subjects were accounted for	No	Yes, study in healthy volunteers
Lapatto-Reiniluoto, 2001	Unclear, no statement was made about allocation and randomization procedure	Yes, blinding impossible by the nature of the procedures	No, all subjects were accounted for	No	Yes, study in healthy volunteers
Neuvonen, 1980	Unclear, no statement was made about	Yes, blinding impossible by	No, all subjects were accounted for	No	Yes, study in healthy volunteers

	allocation and randomization procedure	the nature of the procedures			
Neuvonen, 1983a	Unclear, no statement was made about allocation and randomization procedure	Yes, blinding impossible by the nature of the procedures	No, all subjects were accounted for	Yes, unclear why urinary excretion of only 1 of the 3 drugs was reported	Yes, study in healthy volunteers
Neuvonen, 1983b	Unclear, no statement was made about allocation and randomization procedure	Yes, blinding impossible by the nature of the procedures	No, all subjects were accounted for	No	Yes, study in healthy volunteers
Neuvonen, 1984	Unclear, no statement was made about allocation and randomization procedure	Yes, blinding impossible by the nature of the procedures	No, all subjects were accounted for	No	Yes, study in healthy volunteers
Neuvonen, 1988	Unclear, no statement was made about allocation and randomization procedure	Yes, blinding impossible by the nature of the procedures	No, all subjects were accounted for	Yes, unclear why urinary excretion of only 2 of the 3 drugs was reported	Yes, study in healthy volunteers
Olkkola, 1984	Unclear, no statement was made about allocation and randomization procedure	Yes, blinding impossible by the nature of the procedures	No, all subjects were accounted for	No	Yes, study in healthy volunteers
Wananukul, 2010	Unclear, no statement was made about allocation and randomization procedure	Yes, blinding impossible by the nature of the procedures	No, all subjects were accounted for	No	Yes, study in healthy volunteers, not clear whether SEM or SD was reported, no measure of variability reported for outcomes reported as median

Level of the body of evidence

	High [A]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes and lack of data
Inconsistency	0	
Indirectness	-1	Studies in healthy volunteers
Publication bias	0	
QUALITY (GRADE)	**Low [C]**	

Conclusion	There is limited evidence in favour of activated charcoal, when comparing water intake versus activated charcoal intake:

	It was shown that activated charcoal resulted in a statistically significant decrease of drug uptake, compared to drinking water, immediately after drug intake as well as 5, 15, 30, 60 minutes and 10 h after drug intake (Lapatto-Reiniluoto 1999, Lapatto-Reiniluoto 2000a, Lapatto-Reiniluoto 2000b, Lapatto-Reiniluoto 2001, Neuvonen 1980, Neuvonen 1983a, Neuvonen 1983b, Neuvonen 1984, Neuvonen 1988, Olkkola 1984, Wananukul 2010). Evidence is of low quality and results cannot be considered precise due to limited sample sizes and lack of data.
Reference(s)	**Articles** Lapatto-Reiniluoto O, Kivistö KT, Neuvonen PJ. *Effect of activated charcoal alone or given after gastric lavage in reducing the absorption of diazepam, ibuprofen and citalopram.* Br J Clin Pharmacol. 1999, 48(2):148-53. Lapatto-Reiniluoto O, Kivistö KT, Neuvonen PJ. *Efficacy of activated charcoal versus gastric lavage half an hour after ingestion of moclobemide, temazepam, and verapamil.* Eur J Clin Pharmacol. 2000, 56(4):285-8. Lapatto-Reiniluoto O, Kivistö KT, Neuvonen PJ. *Gastric decontamination performed 5 min after the ingestion of temazepam, verapamil and moclobemide: charcoal is superior to lavage.* Br J Clin Pharmacol. 2000, 49(3):274-8. Lapatto-Reiniluoto O, Kivistö KT, Neuvonen PJ. *Activated charcoal alone and followed by whole-bowel irrigation in preventing the absorption of sustained-release drugs.* Clin Pharmacol Ther. 2001, 70(3):255-60. Neuvonen PJ, Elonen E, Mattila MJ. *Oral activated charcoal and dapsone elimination.* Clin Pharmacol Ther. 1980, 27(6):823-7. Neuvonen PJ, Kannisto H, Hirvisalo EL. *Effect of activated charcoal on absorption of tolbutamide and valproate in man.* Eur J Clin Pharmacol. 1983, 24(2):243-6. Neuvonen PJ, Vartiainen M, Tokola O. *Comparison of activated charcoal and ipecac syrup in prevention of drug absorption.* Eur J Clin Pharmacol. 1983, 24(4):557-62. Neuvonen PJ, Olkkola KT. *Effect of dose of charcoal on the absorption of disopyramide, indomethacin and trimethoprim by man.* Eur J Clin Pharmacol. 1984, 26(6):761-7. Neuvonen PJ, Kivistö K, Hirvisalo EL. *Effects of resins and activated charcoal on the absorption of digoxin, carbamazepine and frusemide.* Br J Clin Pharmacol. 1988, 25(2):229-33. Olkkola KT, Neuvonen PJ. *Do gastric contents modify antidotal efficacy of oral activated charcoal?* Br J Clin Pharmacol. 1984, 18(5):663-9. Wananukul W, Klaikleun S, Sriapha C, Tongpoo A. *Effect of activated charcoal in reducing paracetamol absorption at a supra-therapeutic dose.* J Med Assoc Thai. 2010, 93(10):1145-9.

Poisoning – Inducing vomiting (First Aid)

Question (PICO)	PICO: In people that are poisoned (P), is inducing vomiting as a first aid intervention (I), compared to another first aid intervention or no intervention (C), effective and feasible to influence survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of the symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "poisoning"] OR [mh "poisons"] OR poison*:ti,ab,kw OR intoxica*:ti,ab,kw 2. [mh "vomiting"] OR vomit*:ti,ab,kw OR emesis:ti,ab,kw OR (gastric NEXT evacuation*):ti,ab,kw OR (gastrointestinal NEXT decontamination*):ti,ab,kw 3. #1 AND #2

	MEDLINE (via PubMed interface) for systematic reviews, experimental and observational studies using the following search strategy: 1. "poisoning"[MeSH] OR "poisons"[MeSH] OR poison*[TIAB] OR intoxica*[TIAB] 2. "vomiting"[MeSH] OR vomit*[TIAB] OR emesis[TIAB] OR gastric evacuation*[TIAB] OR gastrointestinal decontamination*[TIAB] 3. "First Aid"[Mesh] OR "Community Health Workers"[Mesh] OR "Emergency Treatment"[Mesh:NoExp] OR "Emergency Medical Services"[Mesh:NoExp] OR "Emergency Service, Hospital"[Mesh] OR "Poison Control Centers"[Mesh] OR "Transportation of Patients"[Mesh] OR "Primary Health Care"[Mesh:NoExp] OR "Acute disease"[Mesh] OR "emergencies" [Mesh] OR "self care"[Mesh] OR "acute management" [TIAB] OR "immediate care" [TIAB] OR "prehospital treatment" [TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'intoxication'/exp OR 'poison'/exp OR poison*:ab,ti OR intoxica*:ab,ti 2. 'vomiting'/exp OR vomit*:ab,ti OR emesis:ab,ti OR (gastric NEXT/1 evacuation*):ti,ab,kw OR (gastrointestinal NEXT/1 decontamination*):ti,ab,kw 3. 'emergency treatment'/de OR 'first aid'/exp OR 'health auxiliary'/exp OR 'emergency care'/de OR 'emergency health service'/exp OR 'poison center'/exp OR 'ambulance'/exp OR 'patient transport'/exp OR 'primary health care'/de OR 'acute disease'/exp OR 'emergency'/exp OR 'self care'/exp OR (acute NEXT/1 manag*):ab,ti OR (prehospital NEXT/1 treat*):ab,ti 4. 1-3 AND Guideline used as source of individual studies: Manoguerra, 2005 (relevant articles were included from the reference list, in addition to individual studies included from the database search)
Search date	25 February2016
In/Exclusion criteria	**Population:** Include: People that are poisoned. Healthy volunteers receiving a non-poisonous drug. **Intervention:** Include: Mechanically or chemically induced vomiting. Exclude: Any other form of first aid management. **Comparison:** Include: Other first aid management, no first aid management. **Outcome:** Include: effectiveness and feasibility of induced vomiting for survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of the symptoms and other health outcomes (including adverse events). **Study design:** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: observational studies if intervention is already included in experimental studies, case series, cross-sectional studies, animal studies, ex vivo or in vitro studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English, French, German, Dutch. **Publication year**: Include: all years.

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison/Risk factor	Remarks
Albertson, 1989, USA	Experimental: Randomised controlled trial	200 mild to moderately poisoned patients, 113 women and 87 men, mean age 30.1±0.8 (SEM), divided into two groups.	Group 1 (n=93): 30 mL syrup of ipecac (with repeat if no response after 30 min) followed by 1 g/kg activated charcoal (AC) after vomiting Group 2 (n=107): 1 g/kg activated charcoal.	
Auerbach, 1986, USA	Experimental: Non-randomised controlled trial	97 intentionally poisoned patients, presenting at the emergency department, > 18 years old, divided in two treatment groups, based on level of consciousness: Group 1: Conscious and willing to drink ipecac Group 2: Lesser degree of consciousness or refusal to drink ipecac	Group 1 (n=51): 30 mL syrup of ipecac mixed with 100 mg thiamine, followed by 400 mL water (with repeat of ipecac if no vomiting after 20 min). Group 2 (n= 37): 100 mg thiamine, gastric lavage through an oral/nasogastric tube (24 French with additional drainage holes, cut by the physician).	
Boxer, 1969, USA	Experimental: Randomised controlled trial	20 salicylate poisoned infants, age range 12-20 months.	Group 1 (n=8): immediate gastric lavage with isotonic saline followed by 15 mL syrup of ipecac (with repeat if no response after 15 min) Group 2 (n=12): immediate 15 mL syrup of ipecac (with repeat if no response after 15 min) followed by gastric lavage with isotonic saline through a nasogastric tube after 30 min.	3 patients from group 2 had no salicylate recovery with both lavage or emesis, and were therefore excluded from the analysis as it was not clear whether they were actually poisoned
Curtis, 1984, USA	Experimental: Randomised controlled trial (within subjects design)	12 healthy volunteers, age range 26-38 years, receiving 24 tablets of 81 mg aspirin.	Group 1: no treatment Group 2: 30 mL syrup of ipecac, followed by 240 mL water with repeat if no vomiting occurred after 30 min Group 3: 60 g AC in 360 mL water and 15 g $MgSO_4$ Group 4: 30 mL syrup of ipecac, followed by 240 mL water with repeat if no vomiting occurred after 30 min. 60 g AC in 360 mL water and 15 g $MgSO_4$, 1.5 h after vomiting [data from group 4 was not extracted]	Group 4: most patients vomited the ingested AC and $MgSO_4$. Therefore, this treatment group was not analysed by the authors. Treatment was started 1h after aspirin intake

Dabbous, 1965, USA	Experimental: Non-randomised controlled trial (within subjects design)	30 poisoned children, mean age 3.2 years	Gagged at home by parents and gagged in hospital by physician after receiving >240 ml carbonated beverage vs 15-20 mL syrup of ipecac after the attempt to gag	
Decker, 1969, USA	Experimental: Randomised controlled trial (within subjects design)	12 male, healthy volunteers, receiving 10 tablets of 0.3 g aspirin	Group 1: no treatment Group 2: 30 g AC via oral administration Group 3: 0.03 mg/pound body weight apomorphine via subcutaneous injection Group 4: a combination of 30 g AC and 0.03 mg/pound body weight apomorphine	Treatment was started 30 min after aspirin intake Serum salicylate concentration was measured after 4, 8, 12 and 24h [Only data from 4h was extracted]
Kornberg, 1991, USA	Experimental: Randomised controlled trial	70 mild to moderately poisoned children, divided into two groups: Group 1: n=32, 17 males, 15 females, mean age 2.5±0.2 years. Group 2: n=38, 22 males, 16 females, mean age 2.3±0.2 years	Group 1: 15 mL syrup of ipecac (with repeat if no response after 30 min), followed by 1 g/kg AC mixed with 40% sorbitol after vomiting, preferably via oral ingestion or alternatively via a nasogastric tube Group 2: immediate administration of 1 g/kg AC mixed with 40% sorbitol, preferably via oral ingestion or alternatively via a nasogastric tube	
Kulig, 1985, USA	Experimental: Randomised controlled trial	630 poisoned patients, of which 592 were treated correctly according to protocol, aged 29.3 years (range 8-80 years), 268 males and 324 females. Group 1 and 2: conscious upon presentation in the ED Group 3 and 4: unconscious, convulsing, intubated or uncooperative upon presentation in the ED	Group 1 (n=214): syrup of ipecac, followed by 30 to 50 g AC, mixed with 20 g $MgSO_4$ and water, orally ingested. Group 2 (n=262): 30 to 50 g AC, mixed with 20 g $MgSO_4$ and water, orally ingested. Group 3 (n=72): gastric lavage with 250 mL aliquots of tap water through an orogatric hose, followed by 30 to 50 g AC, mixed with 20 g $MgSO_4$ and water through a nasogastric tube. Group 4 (n=44): 30 to 50 g AC, mixed with 20 g $MgSO_4$ and water through a nasogastric tube.	

			[Only data from group 1 and group 2 was extracted]	
McNamara, 1989, USA	Experimental: Randomised controlled trial (within subjects design)	10 male, healthy volunteers, aged 18-35 years, ingesting 3 g acetaminophen (37.5 tablets) with 120 mL water	Group 1: no treatment Group 2: 30 mL syrup of ipecac, followed by 240 mL water Group 3: 50 g AC mixed with 70% sorbitol and followed by 240 mL water	A power analysis was performed to detect a 15% difference with a power of 0.8 and a variance of 100. Treatment was started 1h after aspirin intake
Neuvonen, 1983, Finland	Experimental: Randomised controlled trial (within subjects design)	6 healthy volunteers, aged 27-40 years, ingesting 4 tablets, consisting of 1000 mg paracetamol, 500 mg tetracycline and 350 mg aminophylline with 100 mL water	Group 1: 300 mL water, 5 min after ingestion Group 2: 50 g AC in a 300 mL suspension, 5 min or 30 min after ingestion Group 3: 20 mL syrup of ipecac and 300 mL water, 5 min or 30 min after ingestion	Data from urinary excretion of tetracycline was not extracted
Neuvonen, 1984, Finland	Experimental: Randomised controlled trial (within subjects design)	7 healthy volunteers, 3 male and 4 female, 19-29 years, ingesting 20 mg metoclopramide (2 tablets) with 200 mL water, followed by 400 mg cimetidine (2 tablets) and 10 mg pindolol (2 tablets) with 100 mL water	Group 1: 400 ml water Group 2: 50 g AC in a 400 mL suspension Group 3: 20 mL syrup of ipecac and 400 mL water	Treatment was started 5 min after cimetidine/pindolol intake
Saetta, 1991a, UK	Experimental: Non-randomised controlled trial	60 poisoned patients, orally ingesting 20 radioopaque polythene pellets	Group 1 (n=20): No gastric emptying procedure, followed by an X-ray scan Group 2 (n=20): Gastric lavage, followed by an X-ray scan Group 3 (n=20): 30 mL syrup of ipecac with liberal amounts of water, followed by an X-ray scan	
Saetta, 1991b, UK	Experimental: Randomised controlled trial	30 poisoned patients, subdivided in 2 groups: Group 1 (n=17): Aged 16-72 years, 3 males and 4 females Group 2 (n=13): Aged 16-72 years, 2 males and 11 females	Group 1: Gastric lavage with a 33 french orogastric tube and 200-300 mL aliquots of water until the return was clear for 3 consecutive cycles Group 2: 30 mL ipecac mixture (containing 1.8 mL ipecac extract)	
Saincher, 1997, Canada	Experimental: Randomised controlled trial (within subjects design)	10 healthy volunteers, aged 27.7±4 years, receiving 3900 mg acetaminophen (12 tablets) and 250 mL water	Group 1: No intervention Group 2: 30 mL syrup of ipecac, 5 min after ingestion	

			Group 3: 30 mL syrup of ipecac, 30 min after ingestion Group 4: 30 mL syrup of ipecac, 60 min after ingestion	
Tandberg, 1986, USA	Experimental: Randomised controlled trial (within subjects design)	18 healthy volunteers, 30±4.7 years, 11 male and 7 female, receiving 25 100 µg tablets of cyanocobalamin, corresponding to 108.7 µg cobalt tracer, with 250 mL water	Group 1: 30 mL syrup of ipecac and 1 L of water Group 2: lavage with 250 mL aliquots of saline, applied via a 30 french orogastric tube with additional drainage holes, with a total of 3 L	Treatment started 10 min after tracer ingestion
Tenenbein, 1987, USA	Experimental: Randomised controlled trial (within subjects design)	10 healthy volunteers, 21-28 years, 9 males and 1 female, receiving 5 g ampicillin (20 tablets) with 250 mL water	Group 1: no treatment Group 2: gastric lavage with aliquots of 200 mL water, via a 34 gauge orogastric tube, with a minimum total of 2 L Group 3: 50 g AC with 30 g of $MgSO_4$ Group 4: 30 ml syrup of ipecac with 250 mL water, with repeat if vomiting did not occur after 20 min	Treatment started 60 min after drug ingestion
Underhill, 1990, UK	Experimental: Randomised controlled trial	60 paracetamol overdose patients who ingested 5 or more grams of paracetamol and presented within 4h after ingestion, 16-62 years, 16 males and 44 females	Group 1 (n=5): no treatment Group 2 (n=14): gastric lavage with a 36 french orogastric tube Group 3 (n=20): AC in an 10:1 ratio compared to the ingested drug Group 4 (n=21): 30 mL syrup of ipecac, repeated if no vomiting occured after 30 min	Group 1 was discontinued for ethical reasons, as it became clear that plasma levels of paracetamol kept rising without emergency treatment
Young, 1993, USA	Experimental: Non-randomised controlled trial (within subjects design)	19 healthy volunteers, 19-40 years, 14 male and 5 female, ingesting 30 capsules containing 0.03 to 0.26 mCi TC^{99m} with 75 mL tap water	Group 1: 30 mL syrup of ipecac with 1 L water, repeated if no vomiting occurred after 20 min Group 2: orogastric lavage with 300 mL aliquots of water, via a 40 french orogastric tube, until fluid was clear, followed by a supplemental 1 L lavage	Treatment for group 1 started 5 min after tracer ingestion and for group 2 at the time delay needed to induce vomiting during treatment with ipecac

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Clinical outcomes				
Time spend in emergency department (hours)	Ipecac + AC vs AC	Statistically significant: 6.8±2.89 vs 6.0±2.07 MD: 0.8, 95%CI [0.09;1.51] *	1, 93 vs 107 §	Albertson, 1989

		(p=0.03) *Not in favour of ipecac*		
	Ipecac + AC/sorbitol vs AC/sorbitol	<u>Statistically significant</u>: 4.1±0.2 vs 3.4±0.2 MD: 0.7, 95%CI [0.61;0.79] * (p<0.0001) *In favour of AC*	1, 32 vs 38 §	Kornberg, 1991
# Hospitalized patients	Ipecac + AC vs AC	Not statistically significant: 13/93 vs 12/107 § RR: 1.25, 95%CI [0.60;2.60] * ¥ (p=0.56)	1, 93 vs 107	Albertson, 1989
	Ipecac + AC/sorbitol vs AC/sorbitol	Not statistically significant: 3/32 vs 0/38 § RR: 8.27, 95%CI [0.44;154.42] * ¥ (p=0.16)	1, 32 vs 38	Kornberg, 1991
	Ipecac + AC/$MgSO_4$ vs AC/$MgSO_4$	Not statistically significant: 14/214 vs 19/262 § RR: 0.9, 95%CI [0.46;1.76] * ¥ (p=0.76)	1, 214 vs 264	Kulig, 1985
Time hospitalized (days)	Ipecac + AC vs AC	Not statistically significant: 2.4±5.59 vs 1.7±5.17 MD: 0.7, 95%CI [-0.83;2.23] * ¥ (p=0.37)	1, 93 vs 107 §	Albertson, 1989
Admitted to ICU		Not statistically significant: 6/93 vs 5/107 § RR: 1.38, 95%CI [0.44;4.38] * ¥ (p=0.58)		
Time in ICU (days)		Not statistically significant: 1.8±3.86 vs 1.0±0.0 £ † (p>0.05)		
Complications		<u>Statistically significant:</u> 5/93 vs 1/107 § RR: 5.75 ££ † (p<0.05) *In favour of AC*		
Hours in ED before receiving AC	Ipecac + AC/sorbitol vs AC/sorbitol	<u>Statistically significant</u>: 2.6±0.1 vs 0.9±0.1 MD: 1.7, 95%CI [1.65;1.75] * (p<0.0001) *In favour of AC*	1, 32 vs 38 §	Kornberg, 1991
Proportion of patients that were symptomatic patients and showed improvement while in the ED		Not statistically significant: 9/11 vs 7/8 § RR: 0.94, 95%CI [0.64;1.37] * ¥ (p=0.73)		
	Ipecac + AC/$MgSO_4$ vs AC/$MgSO_4$	Not statistically significant: 211/214 vs 260/262 § RR: 0.99, 95%CI [0.97;1.01] * (p=0.51)	1, 214 vs 264	Kulig, 1985
Proportion of children vomiting	Gagging at home vs ipecac	2/15 vs 30/30 § RR: 0.16 ££ †	1, 15 vs 30 (within subjects design)	Dabbous, 1965
	Gagging at hospital vs ipecac	2/30 vs 30/30 § RR: 0.08 ££ †	1, 30 vs 30 (within subjects design)	
Drug recovery from stomach				
Percentage of thiamine recovered	Ipecac vs lavage	<u>Statistically significant</u>: 50±35 vs 90±34 MD: -40, 95%CI [-54.57;-25.43] (p<0.001)	1, 51 vs 37 §	Auerbach, 1986

		In favour of gastric lavage		
Ratio of the amount of salicylate recovered from stomach	Ipecac/Lavage vs Lavage/Ipecac	Statistically significant: 2.02±3.12 vs 0.16±0.15 ¤ MD: 1.86 ££ † (p<0.01) *In favour of ipecac followed by lavage*	1, 8 vs 9 §	Boxer, 1969
Amount of salicylate recovered from stomach (mg)	Ipecac vs lavage	Not statistically significant: 143.63±83.09 vs 83.75±47.75 MD: 59.89 ££ † (p=0.09)		
Amount of cobalt tracer recovery from stomach (µg)		Statistically significant: 30.8±18.8 vs 48.9±14.5 MD: -18.1 ££ † (p<0.005) *In favour of lavage*	1, 18 vs 18 § (within subjects deisgn)	Tandberg, 1986
Percentage of tracer recovered from stomach		Statistically significant: 54.1±21.3 vs 35.5±21 MD: 18.6 ££ † (p=0.016) *In favour of ipecac*	1, 17 vs 17 § (within subjects design)	Young, 1993
Amount of pellets retained		Not statistically significant: 234/400 vs 207/400 § RR: 1.13, 95%CI [1;1.28] * ¥ (p=0.06)	1, 20 vs 20	Saetta, 1991a
	Ipecac vs no intervention	Statistically significant: 234/400 vs 400/400 § RR: 0.59, 95%CI [0.54;0.64] * (p<0.0001) *In favour of ipecac*		
Amount of pellets in the small intestine		Statistically significant: 92/234 vs 65/400 § RR: 2.42, 95%CI [1.84;3.18] * (p<0.0001) *In favour of control*		
	Ipecac vs lavage	Not statistically significant: 92/234 vs 69/207 § RR: 1.18, 95%CI [0.92;1.51] * ¥ (p=0.2)		
Residual solid left after gastric emptying procedure		Statistically significant: 5/13 vs 15/17 § RR: 0.44, 95%CI [0.21;0.89] * (p=0.02) *In favour of ipecac*	1, 13 vs 17	Saetta, 1991b
Drug concentration in the blood				
Serum salicylate concentration (mg/100 ml)	Apomorphine vs control	Statistically significant: 12±2.53 vs 23±2.42 MD: -11 ££ † (p<0.001) *In favour of apomorphine*	1, 10 vs 12 § (within subjects design)	Decker, 1969
	Apomorphine vs AC	Not statistically significant: 12±2.53 vs 12±1.73 MD: 0 ££ † (p>0.05)		

Serum acetaminophen concentration (AUC, µg/h*ml)	Ipecac vs control	*5 min after drug ingestion* Statistically significant 67±37 vs 206±48 MD: -139 ££ † (p<0.05) *In favour of ipecac* *30 min after drug ingestion* Not statistically significant: 183±78 vs 206±48 MD: -23 ££ † (p>0.05) *60 min after drug ingestion* Not statistically significant: 162±47 vs 206±48 MD: -44 ££ † (p>0.05)	1, 10 vs 10 § (within subjects design)	Saincher, 1997
		Statistically significant: 94.32 vs 119.41 MD: -25.09 £ † (p<0.05) *In favour of ipecac*	1, 10 vs 10 (within subjects design)	McNamara, 1989
	Ipecac vs AC/sorbitol	Not statistically significant: 94.32 vs 88.92 MD: 5.4 £ † (p<0.05)		
Percentage change in plasma paracetamol concentration before and after treatment	Ipecac vs AC	Statistically significant: 40.7±18.26 vs 52.25±13.55 MD: -11.55, 95%CI [-21.36;-1.74] * (p=0.02) *In favour of AC*	1, 21 vs 20 §	Underhill, 1990
	Ipecac vs lavage	Not statistically significant: 40.7±18.26 vs 39.33±14.67 MD:1.37, 95%CI [-9.59;12.33] * (p=0.81)	1, 21 vs 14 §	
Peak serum paracetamol concentration (mg/L)	Ipecac vs control	*5 min after drug ingestion* Statistically significant: 4.4±3.67 vs 14±4.89 MD: -10.5 ££ † (p<0.01) *In favour of ipecac* *30 min after drug ingestion* Not statistically significant: 15.2±7.84 vs 14±4.89 MD: 0.3 ££ †	1, 6 vs 6 (within subjects design) §	Neuvonen, 1983
	Ipecac vs AC	*5 min after drug ingestion* Not statistically significant: 4.4±3.67 vs 2.6±2.69 § MD: 1.8 ££ † *30 min after drug ingestion* Not statistically significant: 15.2±7.84 vs 13.9±5.88 MD: 1.3 ££ †		

Peak serum tetracycline concentration (mg/L)	Ipecac vs control	*5 min after drug ingestion* Statistically significant: 0.8±0.73 vs 3.3±0.98 § MD: -2.5 ££ † (p<0.01) *In favour of ipecac* *30 min after drug ingestion* Statistically significant: 2.1±0.98 vs 3.3±0.98 § MD: -1.2 ££ † (p<0.01) *In favour of ipecac*		
	Ipecac vs AC	*5 min after drug ingestion* Statistically significant: 0.8±0.73 vs 0.1±0.01 § MD: 0.7 (p<0.05) *In favour of AC* *30 min after drug ingestion* Statistically significant: 2.1±0.98 vs 1.2±0.73 § MD: 0.9 ££ † (p<0.01) *In favour of AC*		
Peak serum theophylline concentration (mg/L)	Ipecac vs control	*5 min after drug ingestion* Statistically significant: 1.7±1.71 vs 4.0±1.47 § MD: -2.3 ££ † (p<0.05) *In favour of ipecac* *30 min after drug ingestion* Not statistically significant: 3.7±2.45 vs 4.0±1.47 § MD: -0.3 ££ † (p>0.05)		
	Ipecac vs AC	*5 min after drug ingestion* Not statistically significant: 1.7±1.71 vs 1.2±0.49 § MD: 0.5 ££ † (p>0.05) *30 min after drug ingestion* Statistically significant: 3.7±2.45 vs 2.1±1.22 § MD: 1.6 ££ † (p<0.05) *In favour of AC*		
Peak serum cimetidine concentration (mg/L)	Ipecac vs control	Statistically significant: 0.65±0.42 vs 2.53±0.53 § MD: -1.88 ££ † (p<0.01) *In favour of ipecac*	1, 7 vs 7 (within subjects design)	Neuvonen, 1984
	Ipecac vs AC	Statistically significant: 0.65±0.42 vs <0.02 § £ † (p<0.01)		

		In favour of AC		
Serum cimetidine concentration (AUC, mg/h*L)	Ipecac vs control	Statistically significant: 2.18±1.08 vs 8.25±2.25 MD: -6.07 ££ † (p<0.01) *In favour of ipecac*		
	Ipecac vs AC	Statistically significant: 2.18±1.08 vs 0 £ † (p<0.01) *In favour of AC*		
Peak serum pindolol concentration (mg/L)	Ipecac vs control	Statistically significant: 0.023±0.01 vs 0.065±0.02 MD: -0.04 ££ † (p<0.01) *In favour of ipecac*		
	Ipecac vs AC	Statistically significant: 0.023±0.01 vs <0.001 £ † (p<0.01) *In favour of AC*		
Serum pindolol concentration (AUC, mg/h*L)	Ipecac vs control	Statistically significant: 0.15±0.08 vs 0.431±0.17 MD: -0.28 ££ † (p<0.01) *In favour of ipecac*		
	Ipecac vs AC	Statistically significant: 0.15±0.08 vs 0 £ † (p<0.01) *In favour of AC*		
Serum ampicillin concentration (AUC, µg/h*mL)	Ipecac vs control	Statistically significant: 30.9±23.08 vs 50.2±33.83 MD: -19.3 ££ † (p<0.01) *In favour of ipecac*	1, 10 vs 10 §	Tenenbein, 1987
	Ipecac vs AC/$MgSO_4$	Not statistically significant: 30.9±23.08 vs 21.8±7.59 MD: 9.1 ££ † (p>0.05)		
	Ipecac vs lavage	Not statistically significant: 30.9±23.08 vs 34.2±13.6 MD: -3.3 ££ † (p>0.05)		
Drug concentration in urine				
Percentage of salicylate recovered from urine	Ipecac vs control	Statistically significant: 70.2±12.1 vs 96.3±7.5 MD: -26.1 ££ † (p<0.01) *In favour of ipecac*	1, 10 vs 10 § (within subjects design)	Curtis, 1984
	Ipecac vs AC/$MgSO_4$	Statistically significant: 70.2±12.1 vs 56.5±12.5 MD: 13.7 ££ † (p<0.05) *In favour of AC/$MgSO_4$*		
48h Urinary cimetidine excretion (mg)	Ipecac vs control	Statistically significant: 39.7±31.75 vs 157.6±47.89 MD: -117.9 ££ † (p<0.01) *In favour of ipecac*	1, 7 vs 7 (within subjects design)	Neuvonen, 1984

	Ipecac vs AC	Statistically significant: 39.7±31.75 vs 1.3±1.06 MD: 38.4 ££ † (p<0.01) *In favour of AC*		
48h Urinary pindolol excretion (mg)	Ipecac vs control	Statistically significant: 1.22±0.9 vs 2.74±1.22 MD: -1.52 ££ † (p<0.01) *In favour of ipecac*		
	Ipecac vs AC	Statistically significant: 1.22±0.9 vs <0.02 £ † (p<0.01) *In favour of AC*		

Mean ± SD (unless otherwise indicated)
* Calculations done by the reviewer(s) using Review Manager software
¤ SD calculated from available raw data using Microsoft Excel
£ No SD available
†† CI cannot be calculated
¥ Imprecision (large variability of results)
† Imprecision (lack of data)
§ Imprecision (limited sample size or low number of events)

Quality of evidence

Experimental studies in poisoned patients

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Albertson, 1989	Yes, allocation occurred via hospital unit numbers	Yes, blinding impossible by the nature of the procedure	No, all subjects were accounted for	No	Yes, hospital setting
Auerbach, 1968	Yes, non-randomised study design	Yes, blinding impossible by the nature of the procedures	No, all subjects were accounted for	No	Yes, comparison of unconscious and conscious patients suggests different level of intoxication, which might influence treatment efficacy, hospital setting
Boxer 1969	Unclear, randomized through a "previously randomised protocol", but numbers of patients treated in each group are not the same (9 vs 12)	Yes, blinding impossible by the nature of the procedures	No, loss to follow up was accounted for	Yes, no blood salicylate levels, no data on amount salicylate ingested	Yes, Chi^2 test for continuous data is somewhat strange, hospital setting
Dabbous, 1965	Yes, nonrandomized study design	Yes, blinding impossible by the nature of the procedures	No, all subjects were accounted for	No	Yes, hospital setting

Kornberg, 1991	Yes, randomization based on date of presentation	Yes, blinding impossible by the nature of the procedures	No, all subjects were accounted for	No	Yes, hospital setting
Kulig, 1985	Yes, randomization based on date of presentation	Yes, blinding impossible by the nature of the procedures	No, all subjects were accounted for	No	Yes, hospital setting
Saetta 1991 a	Yes, people were included in the control group or a treatment group based on clinical opinion on severity of intoxication	Yes, blinding impossible by the nature of the procedures, although the assessment of X-rays was performed blinded	No, all subjects were accounted for	Yes, no info on clinical outcome of the patients, which could justify the allocation of the patients to the control vs treatment group	Yes, artificial increase in n-value since 20 pellets in 20 volunteers were considered as 400 independent events, indirect evidence for uptake of toxic substances, hospital setting
Saetta 1991 b	Yes, randomization based on date of presentation	Yes, blinding impossible by the nature of the procedures	No, all subjects were accounted for	No	Yes, hospital setting
Underhill, 1999	Unclear, no statement was made about allocation and randomization procedure, but amount of patients differs between treatment groups	Yes, blinding impossible by the nature of the procedures	No, all subjects were accounted for	No	Yes, hospital setting

Level of evidence

	High [A]	Downgrading due to
Limitations of study design	0	
Imprecision	-1	Limited sample sizes, low number of events, lack of data and large variability of results
Inconsistency	0	
Indirectness	-1	Hospital setting
Publication bias	0	
QUALITY (GRADE)	**Low [C]**	

Experimental studies in healthy volunteers

Author, Year	**Lack of allocation concealment**	**Lack of blinding**	**Incomplete accounting of outcome events**	**Selective outcome reporting**	**Other limitations**
Curtis, 1984	Unclear, no statement was made about allocation and randomization procedure	Yes, blinding impossible by the nature of the procedures	No, loss to follow up was accounted for	Yes, no blood salicylate levels	Yes, washout period of only 72 h, study in healthy volunteers

Decker, 1969	Unclear, no statement was made about allocation and randomization procedure	Yes, blinding impossible by the nature of the procedures	Yes, unexplained loss to follow up	No	Yes, washout period of only 3-4 days, study in healthy volunteers
McNamara, 1989	Unclear, no statement was made about allocation and randomization procedure	Yes, blinding impossible by the nature of the procedures, although analysis of the serum samples was performed blinded	No, all subjects were accounted for	No	Yes, study in healthy volunteers
Neuvonen, 1983	Unclear, no statement was made about allocation and randomization procedure	Yes, blinding impossible by the nature of the procedures	No, all subjects were accounted for	Yes, only urinary excretion of 1 of the 3 drugs was reported	Yes, study in healthy volunteers
Neuvonen, 1984	Unclear, no statement was made about allocation and randomization procedure	Yes, blinding impossible by the nature of the procedures	No, all subjects were accounted for	No	Yes, study in healthy volunteers
Saincher, 1997	Unclear, no statement was made about allocation and randomization procedure	Yes, blinding impossible by the nature of the procedures, although analysis of the serum samples was performed blinded	No, all subjects were accounted for	No	Yes, study in healthy volunteers
Tandberg, 1986	Yes, non-randomised design, based on volunteer's convenience	Yes, blinding impossible by the nature of the procedures	No, all subjects were accounted for	No	Yes, study in healthy volunteers, washout period was based on volunteer's convenience
Tenenbein, 1987	Unclear, no statement was made about allocation and randomization procedure	Yes, blinding impossible by the nature of the procedures	No, all subjects were accounted for	No	Yes, study in healthy volunteers
Young, 1993	Yes, nonrandomized design	Yes, blinding impossible by the nature of the procedures	No, loss to follow up was accounted for	No	Yes, study in healthy volunteers

Level of evidence

	High [A]	Downgrading due to
Limitations of study design	-1	See table 'quality of evidence'
Imprecision	-1	Limited sample sizes, low number of events, lack of data and large variability of results
Inconsistency	0	
Indirectness	-1	Study in healthy volunteers
Publication bias	0	
QUALITY (GRADE)	**Very Low [D]**	

Conclusion	*Clinical outcomes:* There is limited evidence in favour of not inducing vomiting: It was shown that ipecac induced vomiting combined with activated charcoal (AC) resulted in a statistically significant increase of time spend in the emergency department (ED), time before receiving AC and the occurrence of complications, compared to receiving AC alone (Albertson 1986, Kornberg 1991). In contrast, a statistically significant decrease of the amount of patients hospitalised, time hospitalised, amount of patients admitted to intensive care unit (ICU), time spend in ICU or the amount of patients showing improvement while in the ED, using ipecac induced vomiting with AC compared to AC alone, could not be demonstrated (Albertson 1986, Kornberg 1991, Kulig 1985). *Drug recovery from stomach* There is conflicting evidence from 6 experimental studies concerning the induction of vomiting: It was shown that ipecac induced vomiting resulted in a statistically significant increase of drug recovery, compared to gastric lavage (Young 1993) and that ipecac induced vomiting resulted in a statistically significant decrease of residual solid in the stomach, compared to gastric lavage (Saetta 1991b). In contrast, it was shown that ipecac induced vomiting resulted in a statistically significant decrease of drug recovery, compared to gastric lavage (Auerbach 1986, Tandberg 1986). Furthermore, a statistically significant increase of drug recovery, using ipecac induced vomiting compared to gastric lavage, could not be demonstrated, while it was shown that the ratio of the amount of recovery using gastric lavage following ipecac induced vomiting was significantly decreased compared to the ratio of the amount of recovery using ipecac induced vomiting following gastric lavage (Boxer 1969). Finally, it was shown that ipecac induced vomiting resulted in a statistically significant decrease of retention of pellets, compared to no treatment, while a statistically significant decrease of retention of pellets using ipecac induced vomiting compared to gastric lavage, could not be demonstrated (Saetta 1991). However, it was shown that ipecac induced vomiting resulted in a statistically significant increase of pellets in the small intestine, compared to no treatment, while a statistically significant increase of pellets in the small intestine compared to gastric lavage, could not be demonstrated (Saetta 1991). *Drug concentration in the blood* There is limited evidence in favour of not inducing vomiting: It was shown that ipecac induced vomiting resulted in a statistically significant increase in drug concentrations in the blood compared to AC (Underhill 1990, Neuvonen 1983, Neuvonen 1984), while a statistically significant increase in drug concentrations in the blood using apomorphine or ipecac induced vomiting compared to AC could not be demonstrated (Decker 1969, McNamara 1989, Tenenbein 1987). Furthermore, a statistically significant decrease of drug concentrations in the blood, using ipecac induced vomiting compared to gastric lavage, could not be demonstrated (Underhill 1990, Tenenbein 1987). It was shown that apomorphine or ipecac induced vomiting resulted in a statistically significant decrease in drug concentrations in the blood compared to no treatment (Decker 1969, McNamara 1989, Neuvonen 1983, Neuvonen 1984, Saincher 1997, Tenenbein 1987),

	however in two studies this effect was only measurable up to 5 minutes after drug ingestion (Neuvonen 1983, Saincher 1997). *Drug concentration in the urine* There is limited evidence in favour of not inducing vomiting: It was shown that ipecac induced vomiting resulted in a statistically significant increase in drug concentrations in the urine compared to AC (Curtis 1984, Neuvonen 1984). On the other hand, it was shown that ipecac induced vomiting resulted in a statistically significant decrease in drug concentrations in the urine compared to no treatment (Curtis 1984, Neuvonen 1984). Evidence is of low to very low quality and results of these studies are imprecise due to limited sample sizes, low numbers of events, lack of data and large variability of results.
Reference(s)	**Articles** Albertson TE, Derlet RW, Foulke GE, Minguillon MC, Tharratt SR. *Superiority of activated charcoal alone compared with ipecac and activated charcoal in the treatment of acute toxic ingestions.* Ann Emerg Med. 1989, 18(1):56-9. Auerbach PS, Osterloh J, Braun O, Hu P, Geehr EC, Kizer KW, McKinney H. *Efficacy of gastric emptying: gastric lavage versus emesis induced with ipecac.* Ann Emerg Med. 1986, 15(6):692-8. Boxer L, Anderson FP, Rowe DS. *Comparison of ipecac-induced emesis with gastric lavage in the treatment of acute salicylate ingestion*. J Pediatr. 1969, 74(5):800-3. Curtis RA, Barone J, Giacona N. *Efficacy of ipecac and activated charcoal/cathartic. Prevention of salicylate absorption in a simulated overdose.* Arch Intern Med. 1984, 144(1):48-52. Dabbous IA, Bergman AB, Robertson WO. *The ineffectiveness of mechanically induced vomiting.* J Pediatr. 1965, 66:952-4. Decker WJ, Shpall RA, Corby DG, Combs HF, Payne CE. *Inhibition of aspirin absorption by activated charcoal and apomorphine.* Clin Pharmacol Ther. 1969, 10(5):710-3. Kornberg AE, Dolgin J. *Pediatric ingestions: charcoal alone versus ipecac and charcoal.* Ann Emerg Med. 1991, 20(6):648-51. Kulig K, Bar-Or D, Cantrill SV, Rosen P, Rumack BH. *Management of acutely poisoned patients without gastric emptying.* Ann Emerg Med. 1985, 14(6):562-7. McNamara RM, Aaron CK, Gemborys M, Davidheiser S. *Efficacy of charcoal cathartic versus ipecac in reducing serum acetaminophen in a simulated overdose.* Ann Emerg Med. 1989 Sep;18(9):934-8. Neuvonen PJ, Olkkola KT. *Activated charcoal and syrup of ipecac in prevention of cimetidine and pindolol absorption in man after administration of metoclopramide as an antiemetic agent.* J Toxicol Clin Toxicol. 1984, 22(2):103-14. Neuvonen PJ, Vartiainen M, Tokola O. *Comparison of activated charcoal and ipecac syrup in prevention of drug absorption.* Eur J Clin Pharmacol. 1983,24(4):557-62. Saetta JP, March S, Gaunt ME, Quinton DN. *Gastric emptying procedures in the self-poisoned patient: are we forcing gastric content beyond the pylorus?* J R Soc Med. 1991, 84(5):274-6. Saetta JP, Quinton DN. *Residual gastric content after gastric lavage and ipecacuanha-induced emesis in self-poisoned patients: an endoscopic study.* J R Soc Med. 1991, 84(1):35-8. Saincher A, Sitar DS, Tenenbein M. *Efficacy of ipecac during the first hour after drug ingestion in human volunteers.* J Toxicol Clin Toxicol. 1997,35(6):609-15. Tandberg D, Diven BG, McLeod JW. *Ipecac-induced emesis versus gastric lavage: a controlled study in normal adults.* Am J Emerg Med. 1986, 4(3):205-9. Tenenbein M, Cohen S, Sitar DS. *Efficacy of ipecac-induced emesis, orogastric lavage, and activated charcoal for acute drug overdose.* Ann Emerg Med. 1987,16(8):838-41. Underhill TJ, Greene MK, Dove AF. *A comparison of the efficacy of gastric lavage, ipecacuanha and activated charcoal in the emergency management of paracetamol overdose.* Arch Emerg Med. 1990, 7(3):148-54. Young WF Jr, Bivins HG. *Evaluation of gastric emptying using radionuclides: gastric lavage versus ipecac-induced emesis.* Ann Emerg Med. 1993, 22(9):1423-7.

	Guidelines Manoguerra AS, Cobaugh DJ; Guidelines for the Management of Poisoning Consensus Panel. *Guideline on the use of ipecac syrup in the out-of-hospital management of ingested poisons.* Clin Toxicol (Phila). 2005, 43(1):1-10.

Poisoning – Safe storage (Prevention)

Question (PICO)	In children (P) is safe storage of poisonous items (I) compared to not doing this (C) effective to prevent poisoning (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Poisoning"] OR poisoning:ti,ab 2. [mh "Product packaging"] OR stor*:ti,ab OR packag*:ti,ab,kw OR "child-resistant":ti,ab,kw OR container:ti,ab,kw OR label*:ti,ab 3. 1 AND 2 **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Poisoning"[Mesh] OR poisoning[TIAB] 2. "Product Packaging"[Mesh] OR stor*[TIAB] OR packag*[TIAB] OR "child-resistant"[TIAB] OR container[TIAB] OR label*[TIAB] 3. "Infant"[Mesh] OR "Child"[Mesh] OR child*[TIAB] 4. "Accident Prevention"[Mesh] OR "Primary Prevention"[Mesh:NoExp] OR "Health Education"[Mesh] OR "Health Behavior"[Mesh] OR "Preventive Medicine"[Mesh] OR "prevention and control"[Subheading] OR "Health promotion"[Mesh] OR "Risk factors"[Mesh] OR prevention[TIAB] OR risk factor*[TIAB] 5. 1-4 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'intoxication'/exp OR poisoning:ab,ti 2. 'packaging'/exp OR stor*:ab,ti OR packag*:ab,ti OR 'child-resistant':ab,ti OR containter:ab,ti OR label*:ab,ti 3. 'infant'/exp OR 'child'/exp OR child*:ab,ti 4. 'prevention'/exp OR 'health education'/exp OR 'health behavior'/exp OR 'self examination'/de OR 'preventive medicine'/exp OR ***'prevention':lnk OR*** 'risk factor'/exp OR prevention:ab,ti OR (risk NEXT/1 factor*):ab,ti 5. 1-4 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in MEDLINE (via PubMed interface).
Search date	10 August 2015
In/Exclusion criteria	**Population**: Include: children **Intervention**: Include: safe storage of medicine or poisonous items; Exclude: child resistant containers for medicine that is not freely available (since this is not decided by the user, but by the pharmaceutical companies) **Comparison**: Include: no safe storage **Outcome**: Include: prevention of poisoning **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available.

	An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Risk factor	Remarks
Ahmed, 2011, Pakistan	Observational study: case-control study	Cases (n=120): children under 5 years of age with oral ingestion of any noxious substances (any substance that had the potential for toxic effects and included medicines, insecticides, pesticides, petroleum products, household chemicals, and cosmetics), admitted to the emergency rooms of three large tertiary care hospitals Controls (n=360): Controls were selected from the emergency rooms of the same hospitals and comprised children with complaints other than poisoning. Controls were matched for age and sex.	Multiple risk factors [only data concerning risk factors on accessibility of hazardous chemicals and medicines were extracted]	Multivariable conditional logistic regression analysis was done.
Krug, 1994, South Africa	Experimental: non-randomized controlled trial	94 000 people in the study area (Gelukspan district) and 72 000 for the control area (Lehurutshe district). 20 000 child-resistant containers were distributed.	Intervention: distribution of child-resistant containers for paraffin storage Control: no distribution of child-resistant containers	Health education about paraffin poisoning prevention was given in both the control and the study areas
Leblanc, 2006, Canada	Observational study: case-control study	Cases (n=351): children aged 7 years and less who presented with injuries from falls, burns or scalds, ingestions or choking Control (n=351): children who presented during the same period with acute non-injury-related conditions, matched by sex and age	Multiple risk factors [only data concerning risk factors on accessibility of hazardous chemicals and medicines were extracted]	A multivariable conditional logistic regression analysis was made.
Petridou, 1996, Greece	Observational study: case-control study	Cases (n=100): 100 consecutive children brought with poisoning to the emergency clinics of the two university affiliated children's hospitals.	Multiple risk factors [only data concerning risk factors on accessibility of hazardous chemicals	Conditional logistic regression was used.

		Controls (n=200): age, gender, and hospital matched controls chosen from among children brought to the outpatient clinics of these hospitals on the same date.	and medicines were extracted]	

Synthesis of findings

Outcome	Risk factor	Effect Size	#studies, # participants	Reference
Risk of unintentional poisoning	Either chemical or medicines stored safe vs not	Not statistically significant: OR: 1.5, 95%CI [0.8;2.8] ¥£† (p>0.05)	1, 120 vs 360	Ahmed, 2011
	Both chemicals and medicine stored unsafe vs not	Statistically significant: OR: 5.6, 95%CI [1.9;16.7] £† (p<0.05) *With harm for chemicals and medicine stored unsafe*		
	No child-resistant lids on bathroom bottles vs child-resistant lids	Statistically significant: OR: 1.70, 95%CI [1.18;2.44] (p<0.05) £† *With harm for no child-resistant lids on bathroom bottles*	1, 106 vs 74	LeBlanc, 2006
	No child-resistant lids on household cleaning supplies vs child-resistant lids	Not statistically significant: OR: 1.02, 95%CI [0.70–1.48] ¥ (p>0.05) £†	1, 154 vs 153	
	Easy access to bathroom beauty supplies or medications vs not	Not statistically significant: OR: 1.06, 95%CI [0.76–1.47] ¥ (p>0.05) £†	1, 129 vs 125	
	Easy access to household cleaning supplies vs not	Not statistically significant: OR: 1.05, 95%CI [0.77–1.45] ¥ (p>0.05) £†	1, 141 vs 137	
	Use of safe product packaging	Not statistically significant: 27/100 vs 49/200 RR: 1.10, 95%CI [0.74;1.65] ¥ (p=0.64)	1, 100 vs 200	Petridou, 1996
Incidence of paraffin ingestion	Child-resistant containers vs not	Statistically significant: 4.54 ± 3.46 vs 9.80 ± 5.63 MD: -5.26, 95%CI [-5.31;-5.21] (p<0.00001) * *In favour of child-resistant containers*	1, 94000 vs 72000	Krug, 1994

Mean ± SD (unless otherwise indicated)
£ No raw data available
† Imprecision (lack of data)
¥ Imprecision (large variability of results)
* Calculations done by the reviewer using Review Manager software

Risk factors concerning safe storage

Quality of evidence

Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations
Ahmed, 2011	No (matched controls)	No	No (multivariate analysis)	No	
Leblanc, 2006	No (matched controls)	No	No (multivariate analysis)	No	

Petridou, 1996	No (matched controls)	No	No (multivariate analysis)	No	

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Lack of data/large variability in results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Child-resistant containers for paraffin

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Krug, 1994	Yes (no randomization)	Yes	Yes (Questionnaires were completed in only 62% of the cases of poisoning that occurred in the study area during the intervention period. Some questionnaires were answered incompletely. This could be explained by staff shortages and inadequate questioner training.)	No	The population estimates may be inaccurate but the two populations are similar in demographic structure and were considered comparable.

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	0	Low number of events
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Moderate [B]**	

Conclusion(s)	**Risk factors concerning safe storage** It was shown that the following risk factors resulted in a statistically significant increased risk of unintentional poisoning: chemicals and medicine stored unsafe and no child-resistant lids on bathroom bottles (Ahmed 2011, LeBlanc 2006). A statistically significant increased risk of unintentional poisoning in case of the following risk factors could not be demonstrated: either chemical or medicines stored safe, no child-resistant lids on household cleaning supplies, easy access to bathroom beauty supplies or medications, easy access to household cleaning supplies, and use of unsafe product packaging (Ahmed 2011, LeBlanc 2006, Petridou 1996). Evidence is of very low quality and results cannot be considered precise due to lack of data and/or large variability of results. **Child-resistant containers for paraffin** There is evidence in favour of using child-resistant containers for paraffin. It was shown that using child-resistant containers resulted in a statistically significant decreased incidence of paraffin ingestion, compared to not using these (Krug 1994). Evidence is of moderate quality.
Reference(s)	**Articles**

	Ahmed B, Fatmi Z, Siddiqui AR, Sheikh AL. *Predictors of unintentional poisoning among children under 5 years of age in Karachi: a matched case-control study*. Inj Prev 2011, 17(1):27-32 Ahmed B, Fatmi Z, Siddiqui AR. *Population attributable risk of unintentional childhood poisoning in Karachi Pakistan*. PLoS ONE 2011 6:10 (same study as the other study of Ahmed 2011) Krug A, Ellis JB, Hay IT, Mokgabudi NF, Robertson J. *The impact of child-resistant containers on the incidence of paraffin (kerosene) ingestion in children*. S Afr Med J 1994, 84(11):730-4 LeBlanc JC, Pless IB, King WJ, Bawden H, Bernard-Bonnin AC, Klassen T, Tenenbein M. *Home safety measures and the risk of unintentional injury among young children: a multicentre case-control study*. CMAJ 2006, 175(8):883-7 Petridou E, Kouri N, Polychronopoulou A, Siafas K, Stoikidou M, Trichopoulos D. *Risk factors for childhood poisoning: a case-control study in Greece*. Inj Prev 1996, 2(3):208-11

Intravenous drug use – Removing a needle (First Aid)

Question (PICO)	In people with a needle in place (P), does removing the needle by a layperson (I), compared to leaving the needle in place (C), influence tissue healing, functional recovery, pain, complications, time to resumption of usual activities, restoration to the pre-exposure condition, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "needles"] OR needle*:ti,ab,kw 2. [mh "administration, intravenous"] OR intraven*:ti,ab,kw OR [mh "substance abuse, intravenous"] 3. fracture*:ti,ab,kw OR retent*:ti,ab,kw OR remov*:ti,ab,kw 4. [mh "vascular diseases"] OR vascul*:ti,ab,kw OR embol*:ti,ab,kw OR [mh "soft tissue injuries"] OR (tissue NEXT injur*):ti,ab,kw OR (tissue NEXT damage*):ti,ab,kw OR necros*:ti,ab,kw OR [mh "necrosis"] 5. 1-4 AND **MEDLINE** (via PubMed interface) for experimental and observational studies, guidelines and systematic reviews using the following search strategy: 1. "Needles"[MeSH] OR Needle*[TIAB] 2. "administration, intravenous"[MeSH] OR intraven*[TIAB] OR "Substance abuse, intravenous"[MeSH] 3. fractur*[TIAB] OR retent*[TIAB] OR remov*[TIAB] 4. Vascular diseases[MeSH] OR vascul*[TIAB] OR embol*[TIAB] OR "soft tissue injuries"[MeSH] OR tissue injur*[TIAB] OR tissue damage*[TIAB] OR necros*[TIAB] OR necrosis[MeSH] 5. 1-4 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'Needle'/exp OR needle:ab,ti 2. 'intravenous drug administration'/exp OR intraven*:ab,ti OR 'substance abuse'/exp 3. fractur*:ab,ti OR retent*:ab,ti OR remov*:ab,ti 4. 'vascular diseas'/exp OR vascul*:ab,ti OR embol*:ab,ti OR 'soft tissue injury'/exp OR (tissue NEXT/1 injur*):ab,ti OR (tissue NEXT/1 damage*):ab,ti OR necros*:ab,ti OR 'necrosis'/exp 5. 1-4 AND
Search date	14 March 2016
In/Exclusion criteria	**Population:** Include: Subjects receiving an intravenous injection of an exogenous substance. **Intervention:** Include: Keeping the needle in place.

	Comparison: Include: Not keeping the needle in place. **Outcome:** Include: Adverse events induced by keeping the needle in place. Exclude: Adverse events induced by keeping the needle in place for >1 h. **Study design:** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: observational studies if intervention is already included in experimental studies, case series, cross-sectional studies, animal studies, ex vivo or in vitro studies, conference abstracts unless no other relevant data is available, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Intravenous drug use – Removing a tourniquet (First Aid)

Question (PICO)	In intravenous drug users with a tourniquet in place (P), does removing the tourniquet (I) change survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms (O), compared to not removing the tourniquet (C)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "substance abuse, intravenous"] OR [mh "poisoning"] OR poison*:ti,ab,kw OR [mh "street drugs"] OR (street NEXT drug*):ti,ab,kw OR (recreational NEXT drug*):ti,ab,kw OR (illicit NEXT drug*):ti,ab,kw OR (abuse NEXT drug*):ti,ab,kw 2. [mh "tourniquets"] OR tourniquet*:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies, guidelines and systematic reviews using the following search strategy: 1. "Substance abuse, intravenous"[MeSH] OR "Poisoning"[MeSH] OR poison*[TIAB] OR "Street drugs"[MeSH] OR "street drug*"[TIAB] OR "recreational drug*"[TIAB] OR "illicit drug*"[TIAB] OR Abuse drug*[TIAB] 2. "Tourniquets"[MeSH] OR "tourniquet*"[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy:

	1. 'substance abuse'/exp OR 'intoxication'/exp OR poison*:ab,ti OR 'street drug'/exp OR (street NEXT/1 drug*):ab,ti OR (recreational NEXT/1 drug*):ab,ti OR (illicit NEXT/1 drug*):ab,ti OR (abuse NEXT drug*):ab,ti 2. 'tourniquet'/exp OR tourniquet*:ab,ti 3. 1-2 AND
Search date	9 March 2016
In/Exclusion criteria	**Population:** Include: Subjects with a tourniquet, receiving an intravenous injection of an exogenous substance. Exclude: Subjects receiving a tourniquet as a treatment for snakebite. **Intervention:** Include: Removal of the tourniquet. **Comparison:** Include: No removal of the tourniquet. **Outcome:** Include: systemic exposure of the substance, local or systemic symptoms after removal of the tourniquet. Exclude: systemic exposure, local or systemic symptoms while tourniquet is still in place. **Study design:** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: observational studies if intervention is already included in experimental studies, case series, cross-sectional studies, animal studies, ex vivo or in vitro studies, conference abstracts unless no other relevant data is available, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Poisoning – Drinking coffee (First Aid)

Question (PICO)	In people with alcohol intoxication (P) is drinking coffee (I) compared to not drinking coffee (C) effective to decrease the effects of the alcohol (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "alcoholic beverages"] OR [mh "alcohol drinking"] OR alcohol*:ti,ab,kw 2. [mh coffee] OR [mh caffeine] OR coffee:ti,ab,kw OR caffeine:ti,ab,kw 3. #1 AND #2 **MEDLINE** (via PubMed interface) for guidelines and systematic reviews using the following search strategy:

	1. "Alcoholic beverages"[Mesh] OR "Alcohol drinking"[Mesh] OR alcohol*[TIAB] OR ethanol[Mesh:NoExp] 2. "Coffee"[Mesh] OR "caffeine"[Mesh] OR coffee[TIAB] OR caffeine[TIAB] 3. ((((((((((Meta-Analysis as Topic[Mesh])) OR ((meta analy*[TIAB]))) OR ((metaanaly*[TIAB]))) OR ((Meta-Analysis[Publication Type]))) OR ((systematic review*[TIAB] OR systematic overview*[TIAB]))) OR ((Review Literature as Topic[Mesh])))) OR ((cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB]))) OR ((reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB]))) OR ((((selection criteria[TIAB] OR data extraction[TIAB])) AND ((Review[PT]))))) NOT ((Comment[PT] OR Letter[PT] OR Editorial[PT] OR animal[Mesh] NOT (animal[Mesh] AND human[Mesh]))) 4. 1-3 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Alcoholic beverages"[Mesh] OR "Alcohol drinking"[Mesh] OR ethanol[Mesh:NoExp] 2. "Coffee"[Mesh] OR "caffeine"[Mesh] OR coffee[TIAB] OR caffeine[TIAB] 3. (("randomized controlled trial"[PT] OR "controlled clinical trial"[PT] OR "clinical trial"[PT] OR "comparative study"[PT] OR "Cross-Over Studies"[Mesh] OR "Intervention Studies"[Mesh] OR random*[TIAB] OR controll*[TIAB] OR "intervention study"[TIAB] OR "experimental study"[TIAB] OR "comparative study"[TIAB] OR trial[TIAB] OR evaluat*[TIAB] OR "Before and after"[TIAB] OR "interrupted time series"[TIAB]) NOT ("animals"[MH] NOT (animals[MH] AND "humans"[MH]))) 4. 1-3 AND **Embase** (via Embase.com interface) for systematic reviews using the following search strategy: 1. 'alcoholic beverage'/exp OR 'drinking behavior'/exp OR alcohol*:ab,ti 2. 'coffee'/exp OR 'caffeine'/exp OR coffee:ab,ti OR caffeine:ab,ti 3. 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti 4. 1-3 AND **Embase** (via Embase.com interface) for intervention studies using the following search strategy: 1. 'alcoholic beverage'/exp OR 'drinking behavior'/exp 2. 'coffee'/exp OR 'caffeine'/exp OR coffee:ab,ti OR caffeine:ab,ti 3. ('randomized controlled trial'/exp OR 'clinical trial'/exp OR 'comparative study'/exp OR random*:ab,ti OR control*:ab:ti OR 'intervention study':ab:ti OR 'experimental study':ab:ti OR 'comparative study':ab:ti OR trial:ab:ti OR evaluat*:ab:ti OR 'before and after':ab:ti OR 'interrupted time series':ab:ti) NOT ('animal'/exp NOT 'human'/exp) 4. 1-3 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in MEDLINE (via PubMed interface).
Search date	6 February 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study

	will be included in case no other evidence with laypeople is available (but considered as indirect evidence). We included studies with intake of alcohol followed by the intake of caffeine. Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. We excluded studies with intake of alcohol mixed with caffeine. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Franks, 1975, Australia	Experimental: Randomized controlled trial	68 volunteers, 31 male, 37 female, aged 20-28 years 4 different treatment groups: alcohol or no alcohol combined with coffee or no coffee (n=17/group) 20 min alcohol or placebo drinking followed by cup of coffee	1. Alcohol + caffeine 2. Alcohol + no caffeine 3. No alcohol + caffeine 4. No alcohol + no caffeine Alcohol = 0.75g/kg ethanol as 20%v/v solution in sugar-free orange squash Placebo = sugar-free orange squash Caffeine = 300mg/70kg dissolved in proven decaffeinated coffee No caffeine = decaffeinated coffee [data about "no alcohol" were not extracted]	
Mackay, 2002, UK	Experimental: Randomized controlled trial	64 volunteers (42 females, 22 males, mean age 21.3 years) Parallel groups design (n=16 in each group) 10 min alcohol or alcohol-placebo drinking – 20 min absorption time – 10	1. Alcohol + caffeine 2. Alcohol + no caffeine 3. No alcohol + caffeine 4. No alcohol + no caffeine Alcohol = 37.5% vodka in quantity of 2.2 ml/kg body weight No alcohol = water submitted for alcohol	The alcohol quantity was calculated to produce a blood alcohol level (BAC) of ± 80 mg/100 ml.

		min coffee drinking (caffeinated or decaffeinated) – 20 min absorption time – performance testing (four choice reaction time testing (FCRT) and digit symbol substitution task (DSST)).	Caffeine = 110-120 mg caffeine per cup, made up to 170 ml with hot water No caffeine: decaffeinated coffee in the same quantity. The rim of each drinking glass was smeared with vodka and peppermint breath freshener was sprayed into each glass to mask the taste and to present an initial, possibly misleading, olfactory clue. [data about "no alcohol" were not extracted]	
Marsden, 2000, UK	Experimental: Randomized controlled trial (within subjects design)	12 male subjects, aged 35-52 years Performance assessed during following tasks: visual search, search and location of items on a navigational chart (chartsearch) and solving of maritime navigational problems (Navtask)	1. Control = no caffeine/no alcohol 2. Alcohol + no caffeine 3. No alcohol + caffeine 4. Alcohol + caffeine Alcohol = 75 ml of whiskey at a strength of 40% by volume Coffee = 250 mg black coffee without sugar [data about "no alcohol" or "caffeine alone" were not extracted]	Cross-over design: subjects were allocated randomly to one of four groups such that each group underwent each condition in different order. Order of tasks was begin counterbalanced across subjects.
Nuotto, 1982, Finland	Experimental: Randomized controlled trial (within subjects design)	20 male subjects, aged 21.3±1.2 years Study 1 (n=10) 15 min tests – 30 min alcohol drinking – 15 min tests – 10 min coffee (+ or – caffeine) drinking – tests – 10 min rest – tests Study 2 (n=10) 15 min tests – 30 min alcohol or placebo drinking – 15 min tests – 10 min coffee drinking (+ or – caffeine) – 15 min tests – 10 min coffee drinking (+ or – caffeine) – tests	Study 1: 1. Alcohol + caffeine 2. Alcohol + no caffeine Alcohol = 300ml juice + ethyl alcohol (1.0 mg/kg body weight) Coffee = instant coffee with or without added caffeine Study 2: 1. Alcohol + caffeine 2. Alcohol + no caffeine 3. No alcohol + caffeine 4. No alcohol + no caffeine Alcohol = 0.7 or 1.5 mg/kg body weight alcoholic bitter No alcohol = non-alcoholic taste-matched bitter Coffee = instant coffee with or without added caffeine [data about "no alcohol" were not extracted]	
Oborne, 1983, UK	Experimental: Randomized controlled trial	4 male and 4 female volunteers, aged 19-25 years	1. Alcohol + caffeine 2. Alcohol + no caffeine 3. No alcohol + caffeine	The amount of alcohol corresponds

	(within subjects design)	First alcoholic or non-alcoholic beverage followed by caffeine or decaffeinated beverage. 10 min drinking – 10min rest – 40min video watching – tasks to measure response time	4. No alcohol + no caffeine Alcohol = 65.5 degrees proof vodka, 2.2 ml/kg body weight Vodka mixed with orange juice in the ratio 3 parts of orange juice to 1 part vodka. Caffeine (150 mg) = crushed 'pro-plus' tablets mixed with a cup of decaffeinated coffee [data about "no alcohol" were not extracted]	with a BAC of about 80mg/100ml (=legal driving limit in UK)

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Plasma ethanol concentration (mg/100ml)	Alcohol and caffeine vs alcohol and no caffeine	Not statistically significant: 40 min: 91±20.62 vs 92±16.49 MD: -1.00, 95%CI[-13.55; 11.55] (p=0.88)* 100 min: 91±20.62 vs 83±12.37 MD: 8.00, 95%CI[-3.43; 19.43] (p=0.30)* 160 min: 78±20.62 vs 72±12.37 MD: 6.00, 95%CI[-5.43; 17.43] (p=0.30)* (SD was calculated from SE with formula: SD = SE*√n)	1 , 68 (17 in each group) §	Franks, 1975
Standing steadiness (eyes open)		Not statistically significant: Better performance at 40min (p≥0.05) †£		
Complex reaction time		<u>Statistically significant:</u> Better performance at 40min (p<0.05) and 160 min (p<0.01) †£ *In favour of caffeine*		
Visual reaction time		<u>Statistically significant:</u> Better performance at 160min (p<0.05) †£ *In favour of caffeine*		
Auditory reaction time		<u>Statistically significant:</u> Better performance at 160min (p<0.05) †£ *In favour of caffeine*		
Numerical reasoning (correct answers)		Not statistically significant: Better performance at 40 and 160 min (p≥0.05) †£		
Perceptual speed (correct answers)		Not statistically significant: Worse performance at 100 min (p≥0.05) †£		

Verbal fluency		Not statistically significant: Worse performance at all times (p≥0.05) †£		
Mean reaction time during FCRT, fixed sequences		Not statistically significant: p=0.236 †£	1, 64 (16 in each group) §	Mackay 2002
Mean reaction time during FCRT, random sequences		Not statistically significant: p=0.230 †£		
Mean errors during FCRT, fixed sequences		Not statistically significant: (p=0.506) †£		
Mean errors during FCRT, random sequences		Not statistically significant: (p=0.160) †£		
Mean correct responses during DSST		Statistically significant: Antagonism of alcohol's effects by caffeine (p=0.006) †£ *In favour of caffeine*		
Visual search		Not statistically significant: 213.5±43.6 vs 202.2±43.8 MD: 11.3 (p>0.05)	1, 12 vs 12 § (within subjects design)	Marsden, 2000
Chart search		Not statistically significant: 32.0±12.9 vs 32.1±10.0 MD: -0.1 (p>0.05)		
Navtask (accuracy)		Not statistically significant: 9.9±1.6 vs 8.8±2.4 MD: 1.1 (p>0.05)		
Navtask (speed/min)		Not statistically significant: 31.0±6.5 vs 31.5±8.3 MD: -0.5 (p>0.05)		
Psychophysiologic performance		Not statistically significant: No alteration in alcohol-induced impairment (data shown in graph) †	1, 10 vs 10 § (within subjects design)	Nuotto, 1982
Response time during memory task test		Statistically significant: Lower reaction time: (p<0.05)†£ *In favour of no caffeine*	1, 8 vs 8 (within subjects design) §	Oborne, 1983

mean±SD (unless otherwise indicated)
*Calculations done by the reviewer(s) using Review Manager software
¥ Imprecision (large variability of results)
† Imprecision (lack of data)
§ Imprecision (limited sample size or low number of events)
£ No raw data available, effect size and CI cannot be calculated

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Franks, 1975	Unclear, participants were randomly assigned, but not mentioned how randomisation was done	Unclear, Participants were ignorant as to which treatment group they had been assigned, but nothing mentioned on masking of taste	No	No	

Mackay, 2002	Unclear, "randomly allocated" but not specified in the article.	Yes, the rim of each glass was smeared with vodka and peppermint breath freshener was sprayed into each glass. Further taste blinding was achieved by participants sucking a Tyrozet antiseptic throat lozenge.	No	No	
Marsden, 2000	No, subjects were allocated randomly to 1 of 4 groups such that each group underwent each condition in a different order, the order of the tasks being counterbalanced across subjects	Unclear, not specified in the article.	No	No	Within subjects design
Nuotto, 1982	No, balanced randomisation	No, double blind	No	No	Within subjects design
Oborne, 1983	Unclear, "parallel sets of tests presented to subjects in random order", not specified how	No, the subject was unaware of whether or not the alcohol or caffeine was in the drink	No	No	Within subjects design

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/lack of data/large variability of the results
Inconsistency	-1	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [C]**	

Conclusion	There is conflicting evidence concerning alcohol/caffeine interactions. A statistically significant increase/decrease of visual search, chart search, Navtask and psychophysiological performance, in case of alcohol and caffeine use compared to alcohol use only, could not be demonstrated (Marsden 2000, Nuotto 1982). It was shown that alcohol and caffeine use resulted in a statistically significant decrease of complex, visual and auditory reaction time, compared to alcohol use only (Franks 1975, Mackay 2002). At the other hand, it was shown that alcohol and caffeine use resulted in a statistically significant increase of reaction time, compared to alcohol use only (Oborne 1983). Evidence is of very low quality and results cannot be considered precise due to limited sample size and lack of data.
Reference(s)	**Articles** Franks HM, Hagedorn H, Hensley VR, Starmer GA. *The effect of caffeine on human performance, alone and in combination with ethanol*. Psychopharmacologia 1975, 45(2):177-81

	MacKay M, Tiplady B, Scholey AB. *Interactions between alcohol and caffeine in relation to psychomotor speed and accuracy*. Hum Psychopharmacol 2002, 17(3):151-6 Marsden G, Leach J. *Effects of alcohol and caffeine on maritime navigational skills*. Ergonomics 2000, 43(1):17-26 Nuotto E, Mattila MJ, Seppälä T, Konno K. *Coffee and caffeine and alcohol effects on psychomotor function*. Clin Pharmacol Ther 1982, 31(1):68-76 Oborne DJ, Rogers Y. *Interactions of alcohol and caffeine on human reaction time*. Aviat Space Environ Med 1983, 54(6):528-34

Poisoning (bad trip) – Cool environment (First Aid)

Question (PICO)	In people with a bad trip (P), is being in a cool environment (I) compared to no cool environment (C) effective to change functional recovery, complications, time to resumption of usual activities, restoration to the pre-exposure condition, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Hallucinogen"] OR hallucinogen*:ti,ab OR "bad trip":ti,ab 2. ([mh "Hallucinations"] OR hallucination*:ti,ab) AND (drug*:ti,ab OR LSD:ti,ab OR Lysergic acid diethylamide:ti,ab OR [mh "Designer drugs"] 3. [mh "Cold Temperature"] OR cold:ti,ab OR cool*:ti,ab 4. 1 OR 2 5. 3 AND 4 **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Hallucinogens"[Mesh] OR hallucinogen*[TIAB] OR "Bad trip"[TIAB] 2. ("Hallucinations"[Mesh] OR hallucination*[TIAB]) AND (drug*[TIAB] OR LSD[TIAB] OR Lysergic acid diethylamide[TIAB] OR "Designer Drugs"[Mesh]) 3. "Cold Temperature"[Mesh] OR cold[TIAB] OR cool*[TIAB] 4. 1 OR 2 5. 3 AND 4 **Embase** (via Embase.com interface) using the following search strategy: 1. 'psychedelic agent'/exp OR hallucinogen*:ab,ti OR 'bad trip':ab,ti 2. ('hallucination'/exp OR hallucination*:ab,ti) AND (drug*:ab,ti OR LSD:ab,ti OR Lysergic acid diethylamide:ab,ti OR 'designer drug'/exp 3. 'cold'/exp OR cold:ab,ti OR cool*:ab,ti 4. 1 OR 2 5. 3 AND 4
Search date	10 September 2015
In/Exclusion criteria	**Population**: Include: people experiencing a bad trip after taking hallucinogens such as LSD **Intervention**: Include: being in a cool environment **Outcome**: Include: functional recovery, complications, time to resumption of usual activities, restoration to the pre-exposure condition, time to resolution of symptoms **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available.

	Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion(s)	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Poisoning – CO detector (Prevention)

Question (PICO)	In humans (P), is using a CO detector (I) compared to not using this (C) effective to prevent CO poisoning (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Carbon Monoxide Poisoning"] OR "carbon monoxide poisoning":ti,ab OR CO:ti,ab 2. [mh "Protective devices"] OR [mh "Environmental monitoring"] OR alarm:ti,ab OR detector:ti,ab 3. 1 AND 2 **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Carbon Monoxide Poisoning"[Mesh] OR "carbon monoxide"[TIAB] OR CO[TIAB] 2. "Protective Devices"[Mesh] OR "Environmental Monitoring"[Mesh] OR alarm[TIAB] OR detector[TIAB] 3. "Accident Prevention"[Mesh] OR "Primary Prevention"[Mesh:NoExp] OR "Health Education"[Mesh] OR "Health Behavior"[Mesh] OR "Preventive Medicine"[Mesh] OR "prevention and control"[Subheading] OR "Health promotion"[Mesh] OR "Risk factors"[Mesh] OR prevention[TIAB] OR risk factor*[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'carbon monoxide intoxication'/exp OR 'carbon monoxide':ab,ti OR CO:ab,ti 2. 'protective equipment'/exp OR 'environmental monitoring'/exp OR alarm:ab,ti OR detector:ab,ti 3. 'prevention'/exp OR 'health education'/exp OR 'health behavior'/exp OR 'self examination'/de OR 'preventive medicine'/exp OR ***'prevention':lnk OR*** 'risk factor'/exp OR prevention:ab,ti 4. 1-3 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in MEDLINE (via PubMed interface).
Search date	10 August 2015
In/Exclusion criteria	**Population**: Include: adults or children

	Intervention: Include: using a CO detector **Comparison**: Include: not using a CO detector **Outcome**: Include: prevention of CO poisoning **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Clifton, 2001, USA	Observational study: cohort study	All cases of CO poisoning in the US cited in media reports (newspaper, television, and radio) between September 1994 and February 1998 were investigated: 4564 CO exposures	Intervention: 2 cities where a CO detector was mandatory ("CO detector ordinance") Control: 14 regions where a CO detector was not mandatory (no CO detector ordinance)	No information about how many CO detectors where present in houses without CO detector ordinance
Krenzelok, 1996, USA	Observational study: cohort study	All calls received by the City of Pittsburgh 911 Emergency Medical Response Center during the months of January, February, and March, 1995, concerning a CO detector in alarm or regarding possible CO poisoning were investigated: 60 residences with a CO alarm vs 41 residence without CO alarm	Intervention: homes with CO alarm Control: homes without CO alarm	Demographic information, the presence or absence of a CO detector with an audible alarm, the highest CO concentration (ppm), the presence or absence of symptoms, and information about the transport of victims to a hospital were extracted from a form specifically designed for the paramedic to document multiple aspects of a possible CO exposure.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Case fatality rate (number of deaths due to CO poisoning as a fraction of number of CO exposures)	Cities with CO detector ordinance vs cities without CO detector ordinance	Statistically significant: 2/429 vs 42/758 § RR: 0.08, 95%CI [0.02;0.35] (p=0.0006) * *In favour of cities with CO detector ordinance*	1, 429 vs 758	Clifton, 2001
Mean CO concentration (ppm)	CO alarm vs no CO alarm	Not statistically significant: 18.6 ± 24.8 vs 96.6 ± 221.8 MD: -78.00, 95%CI [-157.62;1.62] (p=0.05)	1, 60 vs 41	Krenzelok, 1996
Number of person hospitalized		Statistically significant: 1/60 vs 13/41 RR: 0.05, 95%CI [0.01;0.39] (p=0.004) *In favour of CO alarm*		
Number of homes CO>100ppm		Not statistically significant: 1/60 vs 5/41 RR: 0.14, 95%CI [0.02;1.13] (p=0.06)		

Mean ± SD (unless otherwise indicated)

* Calculations done by the reviewer using Review Manager software

§ Imprecision (low number of events)

Quality of evidence

Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations
Clifton, 2001	Yes (no information about exact number of CO detectors in intervention and control group)	No	Yes	No	Data on CO poisoning fatalities were extracted from media reports, reporting bias possible
Krenzelok, 1996	Yes (no demographic data about house occupants with and without CO alarm)	No	Yes	No	

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Low number of events
Inconsistency	0	
Indirectness	-1	Conclusion about CO detectors is indirect since study is on CO detector ordinances, not on CO detectors as such
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Conclusion(s)	There is limited evidence in favour of CO detectors. It was shown that cities with a CO detector ordinance had a statistically significant decrease of number of deaths due to CO poisoning compared to cities without CO detector ordinance (Clifton 2001). In addition it was shown that CO detectors resulted in a statistically significant decreased number of persons hospitalized as a consequence of CO poisoning (Krenzelok 1996). A statistically significant decrease of the mean CO concentration or the number of homes with a CO concentration > 100 ppm, using a CO alarm compared to not using it could not be demonstrated (Krenzelok 1996). Evidence is of very low quality and results cannot be considered precise due to low number of events.
Reference(s)	**Articles** Clifton JC 2nd, Leikin JB, Hryhorczuk DO, Krenzelok EP. *Surveillance for carbon monoxide poisoning using a national media clipping service*. Am J Emerg Med 2001, 19(2):106-8 Krenzelok EP, Roth R, Full R. *Carbon monoxide ... the silent killer with an audible solution*. Am J Emerg Med 1996, 14(5):484-6

Heat stroke – Drugs or alcohol (Risk Factor)

Question (PICO)	In humans (P) is drugs or alcohol use (RF) a risk factor for heat/sun stroke (O) compared to no drugs or alcohol use (C)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "heat stress disorders"] or "heat stroke":ti,ab,kw or "sun stroke":ti,ab,kw 2. [mh "designer drugs"] OR [mh "street drugs"] OR drug*:ti,ab,kw OR [mh ethanol] OR [mh "alcohol drinking"] OR alcohol:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Heat stroke"[Mesh] OR "heat stress disorders"[Mesh] OR "heat stroke"[TIAB] OR "heatstroke"[TIAB] OR "sunstroke"[TIAB] OR "sun stroke"[TIAB] 2. "Street drugs"[Mesh] OR "designer drugs"[Mesh] OR "ethanol"[Mesh] OR drug*[TIAB] OR alcohol*[TIAB] OR drunkenness[TIAB] OR "alcohol* intoxication"[TIAB] OR "ethanol intoxication"[TIAB] OR "ethanol poisoning"[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'heat stroke'/exp OR 'heatstroke':ab,ti OR 'heat stroke':ab,ti OR 'sunstroke':ab,ti OR 'sun stroke':ab,ti 2. 'street drug'/exp OR 'designer drug'/exp OR drug*:ab,ti OR 'alcohol'/exp OR alcohol:ab,ti OR drunkenness*:ab,ti OR 'ethanol intoxication':ab,ti OR 'ethanol poisoning':ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	13 April 2015

In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages at household level. Exclude: studies specifically intended for industrially specific situations (workplace related) **Risk factor**: Include: modifiable, proximal risk factor with a potential immediate implication for practice that results in primary prevention at the household or community level. Risk factors related to healthy persons. Alcohol or drug use as a risk factor. Exclude: risk factors that lead to interventions with already proven effectiveness. The risk factor that does not precede the outcome. The risk factor is common sense. **Outcome**: Include: health outcome measures **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies. **Language**: Include: English **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Risk factor	Remarks
Kilbourne, 1982, USA	Observational: Case-control study	156 persons with heatstroke and 462 control subjects matched by age, sex and neighbourhood of residence.	- Alcoholism - Use of major tranquilizers and other anticholinergic drugs	
Martin-Latry, 2008, France	Observational: case-control Study	56 patients presenting to emergency department with heat-related pathologies (35 female, 21 male), mean age 83 years (range 64-97) and 1120 controls (20 per case, matched for gender and age)	Use of drugs	Controls were randomly extracted from the Social Security Insurance database: they had to live in the same area, not be hospitalized over the heat wave period and with at least one prescription form submitted for refunding during July 2003

Synthesis of findings

Outcome	Risk factor	Effect Size	#studies, # participants	Reference
Fatal heatstroke	Alcoholism	Statistically significant: RR: 15.02, 95%CI [1.87; 120.43] (p=0.0108) *In favour of alcoholism as a risk factor*	1, 156 vs 462	Kilbourne, 1982
	Use of major tranquilizers and other anticholinergic drugs	Not statistically significant: RR: 2.98, 95%CI [0.97; 9.18] ¥ (p=0.0565)		
Hospitalisation for heat-related pathologies	Anticholinergic drugs	Statistically significant: 7/56 vs 11/1100 OR: 6.0, 95%CI [1.8; 19.6] (p=0.0035) *In favour of anticholinergic drugs as a risk factor*	1, 56 vs 1100	Martin-Latry, 2007

	Antipsychotic drugs	Statistically significant: 11/56 vs 24/1143 OR: 4.6, 95%CI [1.9; 11.2] (p=0.0007) *In favour of antipsychotic drugs as a risk factor*	1, 56 vs 1143	
	Anxiolytic drugs	Statistically significant: 22/56 vs 189/1118 OR: 2.4, 95%CI [1.3; 4.4] (p=0.0051) *In favour of anxiolytic drugs as a risk factor*	1, 56 vs 1118	

Mean ± SD (unless otherwise indicated)
¥ Imprecision (large variability of results)

Quality of evidence

Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations
Kilbourne, 1982	No, controls matched to cases by age, sex and neighbourhood	No	Unclear	No	
Martin-Latry, 2007	No, controls matched to cases by age, sex and neighbourhood	No	Yes, they "were not able to control for a range of possible and plausible confounders"	No	

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	0	
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Conclusion	There is limited evidence from 2 observational studies with harm for alcohol and drug use. It was shown that alcoholism resulted in a statistically significant increased risk of fatal heatstroke, compared to no alcoholism (Kilbourne 1982). It was shown that use of anticholinergic, antipsychotic and anxyolitic drugs resulted in a statistically significant increased risk of hospitalisation for heat-related pathologies, compared to no drug use (Martin-Latry 2007). Evidence is of very low quality.
Reference(s)	**Articles** Kilbourne EM, Choi K, Jones S, Thacker SB, and the Field Investigation Team. *Risk factors for Heatstroke*. JAMA 1982, 247(24):3332-6 Martin-Latry K, Goumy M-P, Latry P, Gabinski C, Bégaud B, Faure I, Verdoux H. *Psychotropic drug use and risk of heat-related hospitalization*. European Psychiatry 2007, 22:335-338

Hypothermia – Alcohol intoxication (Risk Factor)

Question (PICO)	In people (P) is drinking alcohol (I) versus not drinking alcohol (C) a risk factor for hypothermia (O)?
Search Strategy	Databases

	The Cochrane Library (systematic reviews and controlled trials) using the following search strategy: 1. [mh ethanol] OR [mh "alcohol drinking"] OR alcohol:ti,ab,kw 2. [mh hypothermia] OR hypothermia:ti,ab,kw OR [mh "body temperature"] OR 'body temperature':ti,ab,kw 3. #1 AND #2 **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Humans[Mesh] OR adult[Mesh] 2. Ethanol[Mesh:NoExp] OR alcohol[TIAB] OR drunkenness[TIAB] OR "alcohol* intoxication"[TIAB] OR "ethanol intoxication"[TIAB] OR "ethanol poisoning"[TIAB] 3. "Hypothermia"[Mesh] OR hypothermia[TIAB] OR "body temperature"[Mesh] OR "body temperature"[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'human'/exp OR 'adult'/exp 2. 'alcohol'/exp OR alcohol:ab,ti OR drunkenness*:ab,ti OR "ethanol intoxication":ab,ti OR "ethanol poisoning":ab,ti 3. 'hypothermia'/exp OR hypothermia:ab,ti OR 'body temperature'/exp OR 'body temperature':ab,ti Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	3 February 2015
In/Exclusion criteria	**Population:** Include: sick or injured people or healthy volunteers of all ages at household level. Exclude: studies specifically intended for industrially specific situations (workplace related) **Risk factor**: Include: modifiable, proximal risk factor with a potential immediate implication for practice that results in primary prevention at the household or community level. Risk factors related to healthy persons. Exclude: risk factors that lead to interventions with already proven effectiveness. The risk factor that does not precede the outcome. The risk factor is common sense. **Outcome:** Include: health outcome measures **Design:** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year:** Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Risk factor	Remarks
Fox, 1979, Canada	Experimental: Randomized trial (within subjects)	10 healthy men, aged 19-25 (mean age 21.2 ±1.62)	1. Alcohol intake – rest – immersion in cold water 2. Placebo intake – rest – immersion in cold water	Volume of alcohol was calculated to result in an average blood alcohol concentration (BAC)

			Alcohol = 95%(v/v) ethanol-distilled water (volume equal to 1.15ml/kg body weight) in unsweetened orange juice. Placebo = same drink, but volume of 95% ethanol was replaced by distilled water.	of 80 mg/100mL whole blood. Cross-over trial: all subjects performed all randomly assigned treatments.
Franks, 1997, UK	Experimental: Randomized trial (within subjects)	16 healthy subjects, 15 male, 1 female, aged 18-35 years undertook 2 upright seated, head-out immersions in stirred water at 15°C wearing swimming costumes.	1. Alcohol – rest – immersion in cold water 2. Placebo (control) – rest – immersion in cold water One hour before entering the water, 3.7 ml/kg body water of 40% v:v alcohol as vodka (intervention) or an equivalent volume of water (control) was given to drink.	- Volume of alcohol was calculated to result in an average BAC of 120 mg/100 ml. - Order of immersion was counterbalanced, and two immersions were separated by at least 48h.
Graham, 1980, Canada	Experimental: Randomized trial (within subjects)	4 male subjects, aged 18-24 years, followed the same protocol twice (with or without alcohol). Subjects were only wearing bathing suits.	1. Alcohol: 1:1 water:alcohol solution (2.5ml/kg body wt), taste modified with concentrated lemon juice 2. Placebo: same volume of water flavoured with lemon juice 15 min fluid ingestion – 15 min rest – 24 min water immersion (13±0.01°C) – 24 min recovery in room air (22.5±1.0°C)	- Each subject was tested on 2 occasions, one day alcohol, other day placebo. - $T_{mean} = 0.67T_{core} + 0.33\ T_{skin}$
Hobson, 1977, Canada	Experimental: Randomized trial (within subjects)	4 subjects (2 male, 2 female), mean age 21 years, were immersed in a cold water bath at 7.5°C after drinking of alcohol, or no alcohol.	1. Alcohol: 1.87 ml of 70-proof whiskey per kilogram of body weight. Drink was given as a 1:2 ratio of whiskey to ginger ale. 2. Placebo: no alcohol. 20 min fluid ingestion – immersion in cold water tank until rectal temperatures reached 35°C	Each subject was tested on 6 occasions within the same 3 month-period and at about the same time of the day.
Keatinge, 1960, UK	Experimental: Randomized trial (within subjects)	10 male subjects were immersed up to the neck in stirred water at 15°C for 30 minutes, wearing only cotton trunks, a helmet and a mask.	1. Alcohol: 75 ml absolute alcohol diluted with 125 ml distilled water 2. Control: nothing fluid ingestion – 45 min rest – 30 min immersion	- Subjects were immersed every second day for 8 days, all immersions were between 2.30 and 4p.m. - Order in which subjects went through experiments was crossed-over in two Latin square

				patterns, 2 subjects went through the experiments in opposite order.
Livingstone, 1980, Canada	Experimental: Randomized trial (within subjects)	Male subjects: (1) controlled environmental chamber at 25°C air temperature and 40% rel. humidity, wearing only shorts (n=4), (2) controlled environmental chamber at 30°C air temperature and 40% rel. humidity, wearing only shorts (n=4), (3) cold environmental room at -23°C dressed in the Canadian Forces Arctic clothing ensemble (n=3), (4) immersed in 25°C water for 1h (n=8, mean age 25±5 years). All experiments were performed with or without alcohol.	(1) – (2): Alcohol: 50 cc of ethanol with orange juice; control: equivalent total volume of orange juice, immediately before exposure (3): Alcohol: 50 cc of ethanol with orange juice; control: equivalent total volume of orange juice; 1.5h before exposure (4) Alcohol: 30cc of ethanol with orange juice; control: equivalent total volume of orange juice; 10 min prior to immersion	
Martin, 1977, Canada	Experimental: Randomized trial (within subjects)	13 subjects (8 males and 5 females) were immersed in water at 13.59±0.13°C for control immersion and 13.58±0.11°C for immersion following alcohol consumption	1. Alcohol: pure ethanol mixed with 200 ml fruit juice 2. Control: no alcohol Alcohol consumed over a 20-min period and immersion followed 45min after beginning of ingestion	An attempt was made to have subjects attain a BAC of ± 80mg/100 ml, but a wide range was found (average of 90-99mg/100 ml)
Martin, 1978, Canada	Experimental: Randomized trial (within subjects)	10 subjects (6 males and 4 females) were immersed in water at 22.17±0.14°C for control immersion vs 21.93±0.16°C for immersion following alcohol consumption	1. Alcohol: pure ethanol mixed with 200 ml fruit juice 2. Control: immersion without alcohol Alcohol consumed over a 20-min period and immersion followed 45min after beginning of ingestion	An attempt was made to have subjects attain a BAC of ± 80mg/100 ml, but a wide range was found (average of 100.6±8.09 mg/100 ml)
Roeggla, 1995, Austria	Experimental: Randomized trial (within subjects)	8 healthy male volunteers (age 21-25) were immersed in water of 20°C for one hour after drinking alcohol or placebo	1. Alcohol: 1L of beverage containing 50g alcohol 2. Placebo: 1L of beverage containing no alcohol	Possibility of any effect of test order or treatment carryover was tested using baseline readings of each period and group. No significant effects were found.

Yoda, 2008, Japan	Experimental: Randomized trial (within subjects)	8 healthy male subjects (mean age 22.3±0.7 years), sat in environmental chamber at 18°C with 50% rel. humidity for 1h after drinking alcohol or placebo.	1. Alcohol: 15vol% alcohol at a dose of 0.36g/kg body weight 2. Placebo: equal volume of distilled water After sitting in chamber for 1 hour while devices were applied, followed by 30 minutes resting for baseline data, subjects drank the alcohol or placebo and remained in a sitting position for 60 min.	Experiments conducted twice for each subject, in randomly chosen order, with a 2 days interval between experiments.

Synthesis of findings

Outcome	Risk factor	Effect Size	#studies, # participants	Reference
Rectal temperature change (°C)	Alcohol vs placebo	Not statistically significant: 3.50±0.97 vs 3.45±1.86 °C/h MD: 0.05 (p≥0.05) £†	1, 10 vs 10 (within subjects) §	Fox, 1979
	Alcohol vs control	Not statistically significant: 1.15°C vs 0.92°C in 20 min MD: 0.23 (p>0.10) £†	1, 13 vs 13 (within subjects) §	Martin, 1977
		Not statistically significant: 0.44°C vs 0.57°C in 20 min MD: -0.13 (p>0.10) £†	1, 10 vs 10 (within subjects) §	Martin, 1978
Fall in rectal temperature (°C)		Not statistically significant: 0.96 vs 0.85 MD: 0.11 (p≥0.05) £†	1, 10 vs 10 (within subjects) §	Keatinge, 1960
	Alcohol vs placebo (immersion in 25°C)	Not statistically significant: 0.5±0.4 vs 0.4±0.3 MD: 0.1 (p≥0.05) £†	1, 8 vs 8 (within subjects) §	Livingstone, 1980
Rectal temperature prior immersion (°C)	Alcohol vs placebo	Not statistically significant: 37.09±0.29 vs 37.11±0.30 MD: -0.02 (p≥0.05) £†	1, 8 vs 8 (within subjects) §	Franks, 1997
		Not statistically significant: 36.8±0.9 vs 36.8±0.2 MD: 0.0 (p≥0.05) £†	1, 4 vs 4 (within subjects) §	Graham, 1980
	Alcohol vs control	Not statistically significant: 37.57 vs 37.65 MD: -0.08 (p≥0.05) £†	1, 10 vs 10 (within subjects) §	Keatinge, 1960
Rectal temperature post immersion +recovery (°C)	Alcohol vs placebo	Not statistically significant: 35.0±0.7 vs 35.4±0.5 MD: -0.4 (p≥0.05) £†	1, 4 vs 4 (within subjects) §	Graham, 1980
Time to cool to rectal temperature of 35°C (min)		Not statistically significant: 58.8±16.1 vs 41.8±7.0 (mean values en SD calculated in excel) MD: 17.0 (p≥0.05) £†	1, 4 vs 4 (within subjects) §	Hobson, 1977
Core temperature change (°C±SEM)	Alcohol vs placebo	Not statistically significant: 0.3±0.15 vs 0.3±0.15 MD: 0.0 (p≥0.05) £†	1, 8 vs 8 (within subjects) §	Yoda, 2008
Aural temperature change (°C)	Alcohol vs control	Not statistically significant: 0.22°C vs 0.11°C MD: 0.11 (p>0.10) £†	1, 13 vs 13 (within subjects) §	Martin, 1977

		Not statistically significant: 0.03°C vs -0.04°C MD: 0.07 (p>0.10) £†	1, 10 vs 10 (within subjects) §	Martin, 1978
	Alcohol vs placebo	<u>Statistically significant:</u> 1.0±0.1°C vs 0.66±0.06°C MD: 0.34, 95%CI[0.14; 0.53], p=0.002 *In favour of placebo*	1, 8 vs 8 (within subjects) §	Roeggla, 1995
Skin temperature changes (°C)		Not statistically significant: 8.2±1.7 vs 8.2±1.7 MD: 0.0 (p≥0.05) £†	1, 8 vs 8 (within subjects) §	Franks, 1997
	Alcohol vs placebo	Not statistically significant: -0.86±0.13 vs -0.84±0.15 MD: -0.02 (p≥0.05) £†	1, 8 vs 8 (within subjects) §	Yoda, 2008
Skin temperature prior immersion (°C)		Not statistically significant: 30.70±2.72 vs 31.34±1.59 MD: -0.64 (p≥0.05) £†	1, 8 vs 8 (within subjects) §	Franks, 1997
		Not statistically significant: 32.0±0.6 vs 31.7±1.2 MD: 0.3 (p≥0.05) £†	1, 4 vs 4 (within subjects) §	Graham, 1980
Skin temperature post immersion + recovery (°C)		Not statistically significant: 27.2±1.8 vs 27.8±1.1 MD: -0.6 (p≥0.05) £†		
Mean body temperature T_{mean} prior immersion (°C)		Not statistically significant: 35.0±0.6 vs 34.9±1.0 MD: 0.1 (p≥0.05) £†		
Mean body temperature T_{mean} post immersion (°C)		Not statistically significant: 28.6±0.2 vs 28.8±0.2 MD: -0.2 (p≥0.05) £†		
Metabolic rate (%)		<u>Statistically significant:</u> Alcohol treatment significantly lowered the MR between 10 and 40 minutes of cold water immersion (p<0.01) *In favour of placebo*	1, 10 vs 10 (within subjects) §	Fox 1979
Metabolic rate (kcal/min)	Alcohol vs control	Not statistically significant: 3.06 vs 3.43 MD: -0.37 (p≥0.05) £†	1, 10 vs 10 (within subjects) §	Keatinge, 1960
Metabolic rate (kcal)	Alcohol vs placebo (immersion in 25°C)	Not statistically significant: 164.2±94.0 vs 147.7±71.0 MD: 16.5 (p≥0.05) £†	1, 8 vs 8 (within subjects) §	Livingstone, 1980
Change in metabolic rate (kcal/m^2/h)	Alcohol vs placebo	<u>Statistically significant:</u> 6.77±3.61 vs no difference MD: 6.77 (p<0.05) £ *In favour of placebo*	1, 8 vs 8 (within subjects) §	Yoda, 2008
Respiratory rate		<u>Statistically significant:</u> Decrease of 9% in first 10sec and 11% in second 10 sec (alcohol vs control) *In favour of placebo*	1, 16 vs 16 (within subjects) §	Franks, 1997

mean±SD (unless otherwise stated)

£ No CI available

† Imprecision (lack of data)

§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Fox, 1979	Yes, within subject design	Yes	No	No	Imprecision (limited sample size, large variability of results, lack of data)
Franks, 1997	Yes, within subject design	Yes, no attempt was made to disguise whether subject was drinking alcohol or control.	No	No	Imprecision (limited sample size, large variability of results, lack of data)
Graham, 1980	Yes, within subject design	Yes	No	No	Imprecision (limited sample size, large variability of results)
Hobson, 1977	Yes, "non-randomized design"	Yes	No	No	Imprecision (limited sample size, large variability of results)
Keatinge, 1960	Yes, within subject design	Yes, subjects were to drink alcohol or nothing	No	No	Imprecision (limited sample size, lack of data)
Livingstone, 1980	Yes, within subject design	Yes	No	No	Imprecision (limited sample size, large variability of results, lack of data)
Martin, 1977	Yes, within subject design	Yes	No	No	Imprecision (limited sample size, lack of data)
Martin, 1978	Yes, within subject design	Yes	No	No	Imprecision (limited sample size, lack of data)
Roeggla, 1995	No, double-blind randomized trial	No	No	No	Imprecision (limited sample size)
Yoda, 2008	Yes, within subject design	Yes	No	No	Imprecision (limited sample size, lack of data)

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/Lack of data
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is limited evidence in favour of not drinking alcohol in case of hypothermia. [In making this evidence conclusion, we place a higher value on 3 significant outcomes in favour of not drinking alchol over other outcomes for which a significant difference could not be shown.]

	It was shown that alcohol consumption resulted in a statistically significant change of metabolic rate, a statistically significant higher change of aural temperature, and a statistical significant decrease in respiratory rate, compared to placebo (Fox 1979, Franks 1997, Roeggla 1995, Yoda 2008). However, a statistically significant change of the following outcomes could not be demonstrated: rectal, skin and core temperature and time to cool to a rectal temperature of 35°C, (Graham 1980, Hobson 1977, Martin 1977, Martin 1978, Keatinge 1960, Livingstone 1980). Evidence is of low quality and results of these studies are imprecise due to limited sample size.
Reference(s)	**Articles** Fox GR, Hayward JS, Hobson GN. *Effect of alcohol on thermal balance of man in cold water*. Can J Physiol Pharmacol 1979, 57(8):860-5 Franks CM, Golden FS, Hampton IF, Tipton MJ. *The effect of blood alcohol on the initial responses to cold water immersion in humans*. Eur J Physiol Occup Physiol 1997, 75(3):279-81 Graham T, Baulk K. *Effect of alcohol ingestion on man's thermoregulatory responses during cold water immersion*. Aviat Space Environ Med 1980, 51(2):155-9 Hobson GN, Collis ML. *The effects of alcohol upon cooling rates of humans immersed in 7.5 degrees C water*. Can J Physiol Pharmacol 1977, 55(3):744-6 Keatinge WR, Evans M. *Effect of food, alcohol, and hyoscine on body-temperature and reflex responses immersed in cold water*. Lancet 1960, 2(7143):176-8 Livingstone SD, Kuehn LA, Limmer RE, Weatherson B. *The effect of alcohol on body heat loss*. Aviat Space Environ Med 1980, 51(9 Pt 2):961-4 Martin S, Diewold RJ, Cooper KE. *Alcohol, respiration, skin and body temperature during cold water immersion*. J Appl Physiol Respir Environ Exerc Physiol 1977, 43(2):211-5 Martin S, Cooper KE. *Alcohol and respiratory and body temperature changes during tepid water immersion*. J Appl Physiol Respir Environ Exerc Physiol 1978, 44(5):683-9 Roeggla G, Roeggla M, Binder M, Roeggla H, Muellner M, Wagner A. *Effect of alcohol on body core temperature during cold-water immersion*. Br J Clin Pract 1995, 49(5):239-40 Yoda T, Crawshaw LI, Saito K, Nakamura M, Nagashima K, Kanosue K. *Effects of alcohol on autonomic responses and thermal sensation during cold exposure in humans*. Alcohol 2008, 42(3):207-12

PROBLEMS WITH HEATH AND COLD

Hypothermia – Active rewarming (First Aid)

Question (PICO)	Among persons with hypothermia (P), is active rewarming (I) compared to no intervention (C) effective to change survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health-related outcomes (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews) using the following search strategy: 1. [mh immersion] OR immersion:ti,ab,kw OR [mh rewarming] OR rewarming*:ti,ab,kw OR [mh exercise] OR exercise*:ti,ab,kw 2. [mh hypothermia] OR hypothermia:ti,ab,kw OR [mh hypothermia, induced] OR [mh shivering] OR [mh chills] OR shivering*:ti,ab,kw 3. [mh randomized controlled trial] OR [mh clinical trial] OR [mh controlled clinical trial] OR [mh cross-over studies] OR [mh intervention studies] OR random*:ti,ab,kw OR control*:ti,ab,kw OR 'intervention study':ti,ab,kw OR 'experimental study':ti,ab,kw OR 'comparative study':ti,ab,kw OR trial:ti,ab,kw OR evaluat*:ti,ab,kw OR 'before and after':ti,ab,kw OR 'interrupted time series':ti,ab,kw 4. 1-3 AND **Embase** (via Embase.com interface) for systematic reviews using the following search strategy: 1. 'immersion'/exp OR immersion*:ab,ti OR 'rewarming'/exp OR rewarming*:ab,ti OR 'exercise'/exp OR exercise*:ab,ti 2. 'hypothermia'/exp OR 'hypothermia':ab,ti OR 'induced hypothermia':ab,ti OR 'shivering'/exp OR shivering*:ab,ti OR 'chill'/exp OR 'cold'/exp 3. ('randomized controlled trial'/exp OR 'clinical trial'/exp OR 'comparative study'/exp OR random*:ab,ti OR control*:ab:ti OR 'intervention study':ab:ti OR 'experimental study':ab:ti OR 'comparative study':ab:ti OR trial:ab:ti OR evaluat*:ab:ti OR 'before and after':ab:ti OR 'interrupted time series':ab:ti) NOT ('animal'/exp NOT 'human'/exp) 4. 1-3 AND **MEDLINE** (via PubMed interface) for systematic reviews using the following search strategy: 1. "immersion"[Mesh] OR immersion*[TIAB] OR "rewarming"[Mesh] OR rewarming*[TIAB] OR "exercise"[Mesh] OR exercise*[TIAB] 2. "Hypothermia" [Mesh] OR "hypothermia" [TIAB] OR "hypothermia, induced"[Mesh] OR "shivering"[Mesh] OR "chills"[Mesh] OR shivering*[TIAB] OR "cold temperature"[Mesh] 3. "randomized controlled trial"[PT] OR "controlled clinical trial"[PT] OR "clinical trial"[PT] OR "comparative study"[PT] OR "Cross-Over Studies"[Mesh] OR "Intervention Studies"[Mesh] OR random*[TIAB] OR controll*[TIAB] OR "intervention study"[TIAB] OR "experimental study"[TIAB] OR "comparative study"[TIAB] OR trial[TIAB] OR evaluat*[TIAB] OR "Before and after"[TIAB] OR "interrupted time series"[TIAB] NOT "animals"[MH] NOT animals[MH] AND "humans"[MH] 4. 1-3 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	06 February 2015

In/Exclusion criteria	**Population:** Include: people with induced hypothermia. Exclude: we excluded studies on patients with hypothermia from other causes than cold water immersion (e.g. therapeutic hypothermia). We excluded animal studies. **Intervention:** Include: rewarming techniques that can be provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). Exclude: We excluded studies on patients with hypothermia that are unconscious. We excluded studies on rewarming techniques used in operative settings, not applicable in the field, that investigate rewarming of neonates and that do not contain spontaneous rewarming (as a control). We excluded animal studies. **Comparison:** Include: studies that compare rewarming techniques that contain (at least) warm water immersion and spontaneous rewarming (as a control) **Outcome:** Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Study design:** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Experimental/observational studies Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies. Experimental/observational studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year:** Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Daanen, 1992, The Netherlands	Experimental: non-randomized trial (within subjects design: cross-over)	Seven subjects with mild hypothermia (27±5 years, 70±8 kg, 175±8 cm)	Intervention: whole body immersion (in 42°C bath or in 42°C bath without hands & feet) or immersion of extremities (hands/feet in 42°C) Control: shivering only (spontaneous rewarming in blankets)	
Giesbrecht, 1994, Canada	Experimental: randomized trial (within subjects design: cross-over)	Six subjects (5 men, 1 woman, 25.8±4.5 years, 177.2±5.4 cm, 75.7±3.3 kg) with mild hypothermia (core temperature >~30°C) were immersed in 8°C water until oesophageal temperature decreased to a mean of 34.6±0.7°C.	Intervention: body-to-body contact (direct contact between the recipient's front and a donor's back inside a double sleeping bag). The subjects were paired with 6 donors (2 men, 4 women) and two subjects acted both as recipient and donor for each other. Control: shivering only (shivering in the supine	Afterdrop was defined as difference between oesophageal temperature on exit from cold water and its nadir. Length of afterdrop was defined as the time between exit from cold water until oesophageal

			position inside a single sleeping bag)	temperature returned to original exit oesophageal temperature. Rate of rewarming was calculated by linear regression for oesophageal temperature data during linear increase after the oesophageal temperature nadir.
Hultzer, 2005, Canada	Experimental: Randomized trial (within subjects design: cross-over)	Six subjects (22.8±3 years, 175.2±10 cm, 75.8±8 kg) with severe hypothermia were cooled in 8°C water for 30 minutes or to a core temperature of 35°C.	Intervention: 30 minutes blanket followed by body-to-body contact. Subjects were removed from the water, dried and insulated for 30 minutes, followed by 120 minutes of direct body-to-body contact with a normothermic partner. Control: 30 minutes blanket	Severe hypothermia is defined as a core temperature <28°C (a human model, using meperidine in mildly hypothermic volunteers to inhibit shivering and simulate the thermal responses of severe hypothermia was used)
Romet, 1988, Canada	Experimental: Randomized trial (within subjects design: cross-over)	Eight subjects with mild hypothermia were cooled for up to one hour in a filled whole-body calorimeter controlled at 22°C.	Intervention: whole body immersion (in 40°C bath) Control: shivering only (spontaneous rewarming in blankets)	
Vanggaard, 1999, Denmark	Experimental: Randomized trial (within subjects design: cross-over)	Six subjects with mild hypothermia	Intervention: Immersion of distal extremities (42°C or 45°C) Control: shivering (subjects were towel dried, placed in a vapour barrier bag within a sleeping bag and then seated in a semirecumbant position)	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Mean afterdrop (°C)	Body-to-body contact vs shivering only	Not statistically significant: 0.54±0.2 vs 0.54±0.2 MD:0 (p>0.05) £†	1, 6 § (within subjects design)	Giesbrecht, 1994
Afterdrop length (minutes)		Not statistically significant: 19.8±8 vs 19.6±6 MD:0.2 (p>0.05) £†		
Rate of rewarming (°C/h)		Not statistically significant: 2.46±1.1 vs 2.40±0.8 MD:0.06 (p>0.05) £†		
Mean afterdrop (°C)	30 minutes blanket followed by body-to-	Not statistically significant: 0.45±0.2 vs 0.44±0.3 MD:0.01 (p>0.05) £†		Hultzer,2005

Rate of rewarming (°C/h)	body contact vs 30 minutes blanket	Statistically significant: 0.52±0.4 vs 0.36±0.4 MD: 0.16 (p<0.05) £ *In favour of 30 minutes blanket followed by body-to-body contact*		
Mean afterdrop (°C)	Whole body immersion 1. in 40°C bath 2. in 42°C bath 3. in 42°C bath without hands & feet vs 4. shivering only	Statistically significant (1 vs 4): 2.2±2.0 vs 4.2±1.2 MD:-2 (p<0.05) £ *In favour of the whole body immersion*	1, 8 § (within subjects design)	Romet 1988
		Not statistically significant (2 vs 4): 0.13±0.12 vs 0.14±0.1 MD:-0.01 (p>0.05) £†	1, 7 § (within subjects design)	Daanen 1992
		Not statistically significant (3 vs 4): 0.18±0.15 vs 0.14±0.1 MD:0.04 (p>0.05) £†		
Afterdrop length (minutes)		Statistically significant (1 vs 4): 6.9±6.1 vs 40.0±19.2 MD:-33.1 (p>0.05) £ *In favour of the whole body immersion*	1, 8 § (within subjects design)	Romet 1988
		Statistically significant (2 vs 4): 5.1±1.9 vs 27.7±8.4 MD:-22.6 (p>0.05) £ *In favour of the whole body immersion*	1, 7 § (within subjects design)	Daanen 1992
		Statistically significant (3 vs 4): 5.0±0.9 vs 27.7±8.4 MD:-22.7 (p<0.05) £ *In favour of the whole body immersion*		
Rate of rewarming (°C/h)		Statistically significant (1 vs 4): 6.16±1.34 vs 0.83±0.33 MD:5.33 (p<0.05) £ *In favour of the whole body immersion*	1, 8 § (within subjects design)	Romet 1988
		Statistically significant (2 vs 4): 10.0±2.6 vs 0.23±0.81 MD:9.77(p<0.05) £ *In favour of the whole body immersion*	1, 7 § (within subjects design)	Daanen 1992
		Statistically significant (3 vs 4): 7.5±1.3 vs 0.23±0.81 MD:7.27 (p<0.05) £ *In favour of the whole body immersion*		
Mean afterdrop (°C)	Immersion of the extremities 1. hands/feet in 42°C 2. hands, forearms, feet, lower legs in 42°C 3. hands, forearms, feet, lower legs in 45°C vs 4. shivering only	Statistically significant (1 vs 4): 0.39±0.24 vs 0.14±0.1 MD:0.25 (p<0.05) £ *In favour of shivering only*	1, 7 § (within subjects design)	Daanen 1992
		Not statistically significant (2 vs 4): 0.4±0.2 vs 0.6±0.4 MD:-0.2 (p>0.05) £†	1, 6 § (within subjects design)	Vanggaard 1999
		Not statistically significant (3 vs 4): 0.4±0.2 vs 0.6±0.4 MD:-0.2 (p>0.05) £†		

Afterdrop length (minutes)		Not statistically significant (1 vs 4): 16.7±12.6 vs 27.7±8.4 MD:-10 (p>0.05) £†	1, 7 § (within subjects design)	Daanen 1992
		Not statistically significant (2 vs 4): 21.2±8.0 vs 20.5±9.4 MD:0.7 (p>0.05) £†	1, 6 § (within subjects design)	Vanggaard 1999
		Not statistically significant (3 vs 4): 14.3±3.9 vs 20.5±9.4 MD:-6.2 (p>0.05) £ *In favour of immersion of the extremities*		
Rate of rewarming (°C/h)		Not statistically significant (1 vs 4): 0.69±0.47 vs 0.23±0.81 MD:0.46 (p>0.05) £†	1, 7 § (within subjects design)	Daanen 1992
		Statistically significant (2 vs 4): 6.1±1.2 vs 3.4±1.5 MD:2.7 (p<0.05) £ *In favour of immersion of the extremities*	1, 6 § (within subjects design)	Vanggaard 1999
		Statistically significant (3 vs 4): 9.9±3.2 vs 3.4±1.5 MD:6.5 (p<0.05) £ *In favour of immersion of the extremities*		

Mean ± SD (unless otherwise indicated)
£ No CI available
§ Imprecision (limited sample size)
† Imprecision (Lack of data)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Daanen, 1992	No randomisation	No	No	No	Within subjects design
Giesbrecht, 1994	No	No	No	No	Within subjects design
Hultzer, 2005	No	No	No	No	Within subjects design
Romet, 1988	No	No	No	No	Within subjects design
Vanggaard, 1999	No	No	No	No	Within subjects design

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Limited sample size, lack of data
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Moderate [B]**	

Conclusion	Body-to-body contact versus no intervention (shivering only) There is limited evidence neither in favour of body-to-body contact nor shivering only in subjects with mild hypothermia. A statistically significant difference in mean afterdrop, afterdrop length and rate of rewarming, using body-to-body contact compared to shivering only, could not be demonstrated (Giesbrecht 1994). Evidence is of moderate quality and results of these studies are imprecise due to limited sample size. Body-to-body contact followed by the use of a blanket for 30 minutes versus the use of a blanket for 30 minutes. There is limited evidence neither in favour of body-to-body contact followed by use of a blanket for 30 minutes, nor the use of a blanket for 30 minutes in subjects with severe hypothermia. A statistically significant difference in mean afterdrop and rate of rewarming, using body-to-body contact (followed by 30 minutes of blanket) compared to shivering/30 minutes blanket only, could not be demonstrated (Hultzer 2005). However, it was shown that body-to-body contact followed by the use of a blanket for 30 minutes resulted in a statistically significant increased rate of rewarming compared to the use of a blanket for 30 minutes (Hultzer 2005). This mean difference (i.e. 0.16°C/h) was considered as not clinically important. Evidence is of moderate quality and results of these studies are imprecise due to limited sample size. Whole body immersion in warm water versus no intervention (shivering only) There is limited evidence in favour of whole body immersion (in warm water) in subjects with mild hypothermia. It was shown that whole body immersion in warm water (40°C bath or 42°C bath) resulted in a statistically significant decreased afterdrop length, a decreased mean afterdrop and an increased rate of rewarming, compared to shivering only (Romet 1988, Daanen 1992). However, a statistically significant decreased mean afterdrop could not be demonstrated in one study (42°C bath, Daanen 1992). Evidence is of moderate quality and results of these studies are imprecise due to limited sample size. Immersion of the hands/forearms/feet/lower legs (extremities) in warm water (42°C/45°C) versus no intervention (shivering only)We are currently not able to formulate an evidence conclusion, since we are unable to evaluate which outcomes are most clinically relevant and whether the effects are of clinical importance: It was shown that immersion of the hands/forearms/feet/lower legs in warm water (42°C/45°C) resulted in a statistical significant increased rate of rewarming (mean difference of 5-6°C/h) (Vanggaard 1999). A statistically significant decreased mean afterdrop or decreased afterdrop length, using immersion of the hands/forearms/feet/lower legs in warm water (42°C/45°C) compared to shivering only, could not be demonstrated (Vanggaard 1999). Evidence is of moderate quality and results of these studies are imprecise due to limited sample size. Immersion of the hands/feet (extremities) in warm water (42°C) versus no intervention (shivering only) We are currently not able to formulate an evidence conclusion, since we are unable to evaluate which outcomes are most clinically relevant and whether the effects are of clinical importance: it was shown that immersion of the hands/feet in warm water (42°C) resulted in a statistical significant increased mean afterdrop compared to shivering only (mean difference of 0.25°C) (Daanen 1992).

	A statistical significant increased rate of rewarming or decreased afterdrop length, using immersion of the hands/feet in warm water (42°C) compared to shivering only, could not be demonstrated (Daanen 1992). However, Evidence is of moderate quality and results of these studies are imprecise due to limited sample size.
Reference(s)	**Articles** Daanen HA, Van de Linde FJ. *Comparison of four noninvasive rewarming methods for mild hypothermia.* Aviat Space Environ Med 1992,63:1070-1076 Giesbrecht GG, Sessler DI, Mekjavic IB, Schroeder M, Bristow GK. *Treatment of mild immersion hypothermia by direct body-to-body contact.* J Appl Physiol (1985) 1994,76:2373-2379 Hultzer MV, Xu X, Marrao C, Bristow G, Chochinov A, Giesbrecht GG. *Pre-hospital torso-warming modalities for severe hypothermia: a comparative study using a human model.* CJEM 2005,7:378-386 Romet TT, Hoskin RW. *Temperature and metabolic responses to inhalation and bath rewarming protocols.* Aviat Space Environ Med 1988,59:630-634 Vanggaard L, Eyolfson D, Xu X, Weseen G, Giesbrecht GG. *Immersion of distal arsm and legs in warm water (AVA rewarming) effectively rewarms mildly hypothermic humans.* Aviat Space Environ Med 1999,70:1081-1088

Hypothermia – Exercise (First Aid)

Question (PICO)	Among persons with hypothermia (P), is exercise (I) compared to no intervention (C) effective to change survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health-related outcomes (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews) using the following search strategy: 1. [mh immersion] OR immersion:ti,ab,kw OR [mh rewarming] OR rewarming*:ti,ab,kw OR [mh exercise] OR exercise*:ti,ab,kw 2. [mh hypothermia] OR hypothermia:ti,ab,kw OR [mh hypothermia, induced] OR [mh shivering] OR [mh chills] OR shivering*:ti,ab,kw 3. [mh randomized controlled trial] OR [mh clinical trial] OR [mh controlled clinical trial] OR [mh cross-over studies] OR [mh intervention studies] OR random*:ti,ab,kw OR control*:ti,ab,kw OR 'intervention study':ti,ab,kw OR 'experimental study':ti,ab,kw OR 'comparative study':ti,ab,kw OR trial:ti,ab,kw OR evaluat*:ti,ab,kw OR 'before and after':ti,ab,kw OR 'interrupted time series':ti,ab,kw 4. 1-3 AND **Embase** (via Embase.com interface) for systematic reviews using the following search strategy: 1. 'immersion'/exp OR immersion*:ab,ti OR 'rewarming'/exp OR rewarming*:ab,ti OR 'exercise'/exp OR exercise*:ab,ti 2. 'hypothermia'/exp OR 'hypothermia':ab,ti OR 'induced hypothermia':ab,ti OR 'shivering'/exp OR shivering*:ab,ti OR 'chill'/exp OR 'cold'/exp 3. ('randomized controlled trial'/exp OR 'clinical trial'/exp OR 'comparative study'/exp OR random*:ab,ti OR control*:ab:ti OR 'intervention study':ab:ti OR 'experimental study':ab:ti OR 'comparative study':ab:ti OR trial:ab:ti OR evaluat*:ab:ti OR 'before and after':ab:ti OR 'interrupted time series':ab:ti) NOT ('animal'/exp NOT 'human'/exp) 4. 1-3 AND **MEDLINE** (via PubMed interface) for systematic reviews using the following search strategy:

	1. "immersion"[Mesh] OR immersion*[TIAB] OR "rewarming"[Mesh] OR rewarming*[TIAB] OR "exercise"[Mesh] OR exercise*[TIAB] 2. "Hypothermia" [Mesh] OR "hypothermia" [TIAB] OR "hypothermia, induced"[Mesh] OR "shivering"[Mesh] OR "chills"[Mesh] OR shivering*[TIAB] OR "cold temperature"[Mesh] 3. "randomized controlled trial"[PT] OR "controlled clinical trial"[PT] OR "clinical trial"[PT] OR "comparative study"[PT] OR "Cross-Over Studies"[Mesh] OR "Intervention Studies"[Mesh] OR random*[TIAB] OR controll*[TIAB] OR "intervention study"[TIAB] OR "experimental study"[TIAB] OR "comparative study"[TIAB] OR trial[TIAB] OR evaluat*[TIAB] OR "Before and after"[TIAB] OR "interrupted time series"[TIAB] NOT "animals"[MH] NOT animals[MH] AND "humans"[MH] 4. 1-3 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	06 February 2015
In/Exclusion criteria	**Population:** Include: people with induced hypothermia. Exclude: we excluded studies on patients with hypothermia from other causes than cold water immersion (e.g. therapeutic hypothermia). We excluded animal studies. **Intervention:** Include: exercise-related rewarming techniques Exclude: We excluded studies on rewarming techniques that do not contain (at least) exercise **Comparison:** Include: studies that compare exercise-related rewarming techniques and spontaneous rewarming (as a control) **Outcome:** Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Study design:** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies.

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Giesbrecht, 1987, Canada	Experimental: randomized controlled trial (within subjects design)	Six subjects were cooled in 8°C water to a core temperature as low as 33°C (mild hypothermia) (30.3±5.4 years, 177.5±5.2 cm, 77.3±6.4 kg)	Intervention: treadmill exercise (the original work load was set at 1.1 km/h and 4% grade). Subjects were asked to walk at the fastest pace they could comfortably maintain and, at their direction, the speed was increased gradually to 5.6 km/h Control: shivering (subjects were asked to lie on a mattress inside the insulated rescue bag)	
Giesbrecht, 1998, Canada	Experimental: non-randomized	Six subjects were cooled in 8°C	Intervention:	

	controlled trial (within subjects design)	water to a core temperature as low as 35.3±0.7°C (mild hypothermia) (25.2±4.0 years, 175.5±5.9 cm, 77.2±8.4 kg)	1. Exercise (treadmill exercise immediately initiated and gradually increasing in velocity from 2.0 to 4.4 km/h 2. Exercise + shivering (an initial period of shivering until the afterdrop period was complete followed by the same treadmill exercise) Control: Shivering (supine position)	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Mean afterdrop (°C)	Exercise vs shivering only	Statistically significant: 0.91±0.28 vs 0.33±0.24 MD: 0.58 (p<0.05) £ *In favour of shivering only*	1, 6 § (within subjects design)	Giesbrecht 1987
		Statistically significant: 1.10±0.4 vs 0.35±0.30 MD: 0.70 (p<0.05) £ *In favour of shivering only*		Giesbrecht 1998
Afterdrop length (minutes)		Statistically significant: 26.8±10.7 vs 14.0±6.7 MD: 12.8 (p<0.05) £ *In favour of shivering only*		Giesbrecht 1987
		Statistically significant: 31.8±7 vs 16.1±7 MD: 15.7 (p<0.05) £ *In favour of shivering only*		Giesbrecht 1998
Rate of rewarming (°C/h)		Statistically significant: 4.98±0.8 vs 3.45±1.2 MD: 1.53 (p<0.05) £ *In favour of exercise*		Giesbrecht 1987
		Not statistically significant: 3.45±0.7 vs 2.99±1.0 MD: 0.46 (p>0.05) £†		Giesbrecht 1998
Total recovery time (minutes)		Not statistically significant: 48.5±9.3 vs 49.1±8.4 MD: -0.6 (p>0.05) £†		Giesbrecht 1987
Mean afterdrop (°C)	Exercise + shivering versus exercise	Not statistically significant: 0.38±0.3 vs 0.35±0.3 MD: 0.03 (p>0.05) £†		Giesbrecht 1998
Afterdrop length (minutes)		Not statistically significant: 15.8±11.0 vs 16.1±7.0 MD: -0.3 (p>0.05) £†		
Rate of rewarming (°C/h)		Not statistically significant: 2.4±0.8 vs 2.99±1.0 MD: -0.59 (p>0.05) £†		

Mean ± SD (unless otherwise indicated)
£ No effect size/CI available
§ Imprecision (limited sample size)
† Imprecision (Lack of data)

Exercise versus shivering
Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Giesbrecht,1987	No	No	No	No	within subjects design
Giesbrecht,1998	No randomisation	No	No	No	within subjects design

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Limited sample size
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Moderate [B]**	

Exercise+ shivering versus shivering
Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Giesbrecht,1998	No randomisation	No	No	No	within subjects design

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample size
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	Exercise versus no intervention (shivering only) There is limited evidence in favour of shivering only. In making this evidence conclusion, we place a higher value on the outcomes mean afterdrop/afterdrop length over rate of rewarming. It was shown that shivering resulted in a statistically significant decreased mean afterdrop (mean difference 0.60-0.75°C) and a decreased afterdrop length (mean difference of 12-15 minutes) (Giesbrecht 1987, Giesbrecht 1998). However, it was shown that exercise resulted in a statistically significant increased rate of rewarming (mean difference 1.5°C/h) (Giesbrecht 1987), whereas Giesbrecht 1998 was not able to demonstrate a statistical significant difference in rate of rewarming. Finally, one study was not able to demonstrate a statistical significant difference in total recovery time (Giesbrecht 1987). Evidence is of moderate quality and results of these studies are imprecise due to limited sample size. Exercise + shivering versus no intervention (versus shivering only) There is limited evidence neither in favour of the exercise combined with shivering nor shivering only. A statistically significant difference in mean afterdrop, afterdrop length and rate of rewarming, using exercise+shivering compared to shivering only, could not be demonstrated (Giesbrecht 1987, Giesbrecht 1998). Evidence is of low quality and results of these studies are imprecise due to limited sample size.
Reference(s)	**Articles** Giesbrecht GG, Bristow GK, Uin A, Ready AE, Jones RA. *Effectiveness of three field treatments for induced mild (33.0 degrees C) hypothermia*. J Appl Physiol (1985) 1987,63:2375-2379 Giesbrecht GG, Bristow GK. *The convective afterdrop component during hypothermic exercise decreases with delayed exercise onset*. Aviat Space Environ Med 1998,69:17-22

Hypothermia – Special clothing (Risk Factor)

Question (PICO)	In people (P), is wearing special clothing (I) compared to not wearing special clothing (C) a protective factor for hypothermia (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh Hypothermia] OR hypothermia:ti,ab 2. [mh Clothing] OR cloth*:ti,ab 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Hypothermia" [Mesh] OR hypothermia[TIAB] 2. "Clothing"[Mesh] OR clothing[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'hypothermia'/exp OR 'hypothermia':ab,ti 2. 'clothing'/exp OR cloth*:ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).

Search date	16 September 2015
In/Exclusion criteria	**Population:** Include: adults or children; Exclude: neonates, hospitalized people **Intervention:** Include: wearing special clothing as a protection against hypothermia, including thermal insulation, different layers of clothing,… **Comparison:** Include: wearing usual clothing **Outcome:** Include: risk of hypothermia, body temperature **Study design:** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year Country	Study design	Population	Comparison	Remarks
Burthscher, 2012, Austria	Experimental: randomized controlled trial	Nine well-trained healthy sport students (6 male and 3 female participants)	Intervention 1 (n=3): polyester caps and lightweight (200 g) windbreaker Jackets Intervention 2 (n=3): polyester caps, light windbreaker jackets, and pants (both waterproof and breathable, made of polyamide + polyester lining) Control (n=3): T shirt + short pants	Subjects started walking for 1 hour in a climate chamber (0°C ambient temperature and wind speed of 10 km/h) at 70% VO_2 max wearing gloves, a T-shirt, and shorts. Then, the walking speed was reduced to 30% VO_2 max for an additional 60 minutes or until core temperature dropped below 35.5 °C. Subsequently, 3 groups of 3 participants continued walking without change of clothing or wearing additional clothing as described (see "Comparison").

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Core temperature (°C)	Windbreaker jacket + windbreaker pants vs T shirt + short pants	Statistically significant: 36.3 ± 0.1 vs 35.4 ± 0.1 λ MD: 0.70, 95%CI [0.54;0.86] (p<0.00001) * *In favour of windbreaker jacket and windbreaker pants*	1, 3 vs 3 §	Burthscher, 2012
Skin temperature		Statistically significant: 26 ± 1 vs 22 ±1 λ MD: 4, 95%CI [2.40;5.60] (p<0.00001) * *In favour of windbreaker jacket and windbreaker pants*		

Core temperature (°C)	Windbreaker jacket + short pants vs T shirt + short pants	Not statistically significant: 35.3 ± 0.1 vs 35.4 ± 0.1 λ MD: -0.10, 95%CI [-0.26;0.06] (p=0.22) *		
Skin temperature		Not statistically significant: 22.2 ± 1 vs 22 ± 1 λ MD: 0.20, 95%CI [-1.40;1.80] (p=0.81) *		

λ Data extracted from graph

* Calculations done by the reviewer using Review Manager software

§ Imprecision (limited sample size)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Burthscher, 2012	Unclear (no information about mode of randomization, and allocation concealment)	Unclear	No	No	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is limited evidence in favour of using a windbreaker jacket and windbreaker pants. It was shown that wearing a windbreaker jacket and windbreaker pants resulted in a statistically significant increase of core temperature and skin temperature compared to wearing a T shirt and short pants (Burthscher 2012). A statistically significant increase of core temperature and skin temperature using a windbreaker jacket and short pants compared to wearing a T shirt and short pants could not be demonstrated (Burthscher 2012). Evidence is of low quality and results cannot be considered precise due to limited sample size.
Reference(s)	**Articles** Burtscher M, Kofler P, Gatterer H, Faulhaber M, Philippe M, Fischer K, Walther R, Herten A. *Effects of lightweight outdoor clothing on the prevention of hypothermia during low-intensity exercise in the cold*. Clin J Sport Med 2012, 22(6):505-7

Frostbite – Active rewarming (First Aid)

Question (PICO)	In humans with frostbite (P), is active rewarming (I) compared to not rewarming (C) effective to change functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh frostbite] or frostbite:ti,ab,kw or "cold injur*":ti,ab,kw

	MEDLINE (via PubMed interface) for experimental and observational studies using the following search strategy: 1. frostbite[Mesh] OR frostbite[TIAB] OR cold injur*[TIAB] 2. immersion[Mesh] OR immers*[TIAB] OR rewarming[Mesh] OR rewarm*[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. frostbite/exp OR frostbite:ab,ti OR (cold NEXT/1 injur*):ab,ti 2. immersion/exp OR immers*:ab,ti OR rewarming/exp OR rewarm*:ab,ti 3. 1-2 AND
Search date	24 September 2015
In/Exclusion criteria	**Population**: Include: People with frostbite. **Intervention**: Include: rewarming techniques that can be provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). Exclude: studies on rewarming techniques used in operative settings, not applicable in the field, that investigate rewarming of neonates and that do not contain spontaneous rewarming (as a control). We excluded animal studies. **Comparison**: Include: studies that compare rewarming techniques that contain (at least) warm water immersion and spontaneous rewarming (as a control) **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	Not applicable

Frostbite – Irrigation with lukewarm water (First Aid)

Question (PICO)	In people with a sticking frostbite (P), is irrigation with lukewarm water (I) compared to not doing this (C) effective to change functional recovery, complications, time to resumption of usual activities, restoration to the pre-exposure condition, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "Frostbite"] OR frostbite:ti,ab,kw **MEDLINE** (via PubMed interface) using the following search strategy: 11. "Frostbite"[Mesh] OR frostbite[TIAB] 12. "Water"[Mesh] OR water[TIAB] 13. "Hot Temperature"[Mesh] OR warm[TIAB] OR temperature[TIAB] 14. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 11. 'frostbite'/exp OR frostbite:ab,ti 12. 'water'/exp OR water:ab,ti 13. 'heat'/exp OR warm:ab,ti OR temperature:ab,ti 14. 1-3 AND
Search date	9 September 2015
In/Exclusion criteria	**Population**: Include: people with a sticking frostbite **Intervention**: Include: using lukewarm water to release the limb with the frostbite **Outcome**: Include: release of the limb, functional recovery, complications, time to resumption of usual activities, restoration to the pre-exposure condition, time to resolution of symptoms **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion(s)	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Frostbite – Protective emollients (Risk Factor)

Question (PICO)	In humans (P), is the use of protective emollients (RF) a risk factor for frostbite (O) compared to not using protective emollients (C)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh frostbite] or frostbite:ti,ab,kw or "cold injur*":ti,ab,kw 2. [mh emollients] OR emollient*:ti,ab,kw OR [mh ointments] OR ointment*:ab,ti OR salve*:ti,ab,kw OR lotion*:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Frostbite[Mesh] OR frostbite[TIAB] OR cold injur*[TIAB] 2. Emollients[Mesh] OR emollient*[TIAB] OR ointments[Mesh] OR ointment*[TIAB] OR salve*[TIAB] OR lotion*[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. frostbite/exp OR frostbite:ab,ti OR (cold NEXT/1 injur*):ab,ti 2. 'emollient agent'/exp OR emmolient*:ab,ti OR ointment/exp OR ointment*:ab,ti OR salve*:ab,ti OR lotion*:ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	25 September 2015
In/Exclusion criteria	**Population**: Healthy people of all ages. **Intervention**: protective emollients **Comparison**: no emollients **Outcome**: Frostbite **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Risk factor	Remarks
Lehmuskallio, 1995, Finland	Observational: case-control study	Cases: 913 young male conscripts with local frostbite of the head that needed medical attention	Multiple risk factors	

		Controls: 2478 uninjured control conscripts (two conscripts who had not developed frostbite were randomly selected from the same squads as the injured soldiers to act as controls)	[only data on protective emollients are extracted]	

Synthesis of findings

Outcome	Risk factor	Effect Size	#studies, # participants	Reference
Frostbite	Use of protective ointment	Ears: Statistically significant: OR: 4.5, 95%CI [2.0147; 10.0509] (p=0.0002)*£† *With harm for protective ointment* Nose: Statistically significant: OR: 5.6, 95%CI [4.0131; 7.8143] (p<0.0001)*£† *With harm for protective ointment* Other part of face: Not statistically significant: OR: 3.8, 95%CI [0.945; 15.2805] (p=0.0601)*¥ £†	1, 913 vs 2478	Lehmuskallio, 1995

* CI calculated by the reviewer using Review Manager software
£ No raw data available
¥ Imprecision (large variability of results)
† Imprecision (lack of data)

Quality of evidence

Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations
Lehmuskallio, 1995	No	No	No (multivariate analysis)	No	

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	lack of data/large variability of the results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Conclusion	There is limited evidence with harm for using protective emollients. It was shown that using protective emollients resulted in a statistically significant increased risk of frostbite on the ears and nose, compared to not using protective emollients (Lehmuskalllio 1995). A statistically significant increased risk of frostbite on other parts of the face when using protective emollients compared to not using protective emollients could not be demonstrated (Lehmuskalllio 1995). Evidence is of low/very low quality and results cannot be considered precise due to limited sample size, lack of data and/or large variability of results.

Reference(s)	**Articles** Lehmuskallio E, Lindholm H, Koskenvuo K, Sarna S, Friberg O, Viljanen A. *Frostbite of the face and ears: epidemiological study of risk factors in Finnish conscripts*. BMJ 1995, 311:1661-3

Frostbite – Walking on frozen feet (Risk Factor)

Question (PICO)	In humans with frozen feet (P), is continuing to walk (RF) compared to not continuing to walk (C) a risk factor for functional recovery, pain, complications, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh walking] OR walk* 2. ([mh foot] OR foot:ti,ab,kw OR feet:ti,ab,kw) AND (frozen:ti,ab,kw OR freez*:ti,ab,kw) 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 5. Walking[Mesh] OR walk*[TIAB] 6. (Foot[Mesh] OR foot[TIAB] OR feet[TIAB]) AND (frozen[TIAB] OR freez*[TIAB]) 7. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Walking/exp OR walk*:ab,ti 2. (Foot/exp OR foot:ab,ti OR feet:ab,ti) AND (frozen:ab,ti OR freez*:ab,ti) 3. 1-2 AND
Search date	2 February 2016
In/Exclusion criteria	**Population**: Include: people with frozen feet. **Intervention**: Include: continuing to walk on frozen feet. **Comparison**: Include: resting, not continuing to walk on frozen feet. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Heat stroke – Cooling (First Aid)

Question (PICO)	In humans with heat/sun stroke (P), is cooling (I) compared to no cooling (C) effective for laypeople to change survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. Cool*:ti,ab,kw 2. [mh "heat stress disorders"] or "heat stroke":ti,ab,kw or "sun stroke":ti,ab,kw 3. #1 AND #2 **MEDLINE** (via PubMed interface) using the following search strategy: 1. cool*[TIAB] 2. "heat stress disorders"[Mesh] OR "heat stroke"[TIAB] OR "sun stroke"[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'cooling'/exp OR cool*:ab,ti 2. 'heat stroke'/exp OR 'heat stroke':ab,ti OR 'sun stroke':ab,ti 3. 1-2 AND Guidelines, systematic reviews, retrieved with the above searches, and used as source for individual studies: Bouchama, 2007 Newport, 2012 Smith, 2005 Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	12 February 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers.

	Design: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies. **Language**: Include: English **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Armstrong, 1996, USA	Experimental: non-randomized controlled trial	21 hyperthermic distance runners, 4 woman and 17 men, aged 35±3 years, were recorded shortly after they finished the 11.5 km Falmouth Road Race, at the medical aid station. Each patient was diagnosed with extreme hyperthermia and either heat exhaustion or preliminary exertional heatstroke. Subjects were treated with ice water immersion (n=14) or air exposure (n=7)	1. Ice water (1-3°C) immersion of torso and upper legs 2. Air exposure (24.4°C, no fans) with wet towels covering torso and upper legs	
Clapp, 2001, USA	Experimental: Randomized controlled trial (within subjects design)	5 healthy male subjects, aged 21-32 years. Subjects started with 45 min jogging outdoors followed by exercise in heated environmental chamber (wet bulb globe temperature (WBGT) 39±1°C) until the onset of heat strain (typically an additional 30-minute run). The session was terminated when 1) rectal temperature exceeded 38.75°C, 2) HR exceeded 90% of predicted maximum, 3) subject exhibited any evidence of heat stress, or 4) subject chose to stop.	1. Submersion of torso only in a pool of cold water (10-12°C) 2. Submersion of hands and feet only in cold water tubs (10-12°C) 3. Sitting in the shade with no radiant heating and with a 0.67 m/s breeze from a 91 cm fan.	
Clements, 2002, USA	Experimental: Randomized controlled trial (within subjects over design)	17 (3 women, 14 men) highly trained, heat-acclimated distance runners, mean age (±SEM) 28±2years. 20 min equilibration period – average distance run of	1. Ice-water immersion: 5.15±0.20°C 2. Cold-water immersion: 14.03±0.28°C 3. Mock immersion: no water, air temperature =28.88±0.76°C	

		19±0.5 km, ±90 min – immersion for 12 min. After distance run, body weight and T_{re} were measured. Immersion began 2-4 min after completing the distance run.		
Kielblock, 1986, South-Africa	Experimental: Randomized controlled trial (within subjects over design)	5 healthy male subjects, aged 29.0±2.3 years. Initial rest of 1 hr in neutral environment, followed by external work rate of 54 W (block-stepping regimen in a hot, humid environment) until rectal temperatures increased by 2.0°C over individual resting levels. Then, subjects were removed to a neutral environment and cooled by 1 of 5 procedures until rectal temperature returned to resting level.	1. 6 'instant cold packs' (ICPs): 2 at neck, groins and axillae 2. Body covered with ICPs: placed on forehead, neck, shoulders, upper arms, torso and thighs 3. Evaporative cooling: water splashed onto body and evaporated by compressed air 4. Evaporative cooling + 6 ICPs: combination of treatments 1 and 3 5. Passive cooling: subject lies passively face-up on stretcher Each subject was exposed to each cooling procedure	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Cooling rate (°C/min)	1. Ice water immersion 2. Air exposure	<u>Statistically significant:</u> 0.20±0.02 vs 0.11±0.02 MD: 0.09, 95% CI[0.07; 0.11], p<0.00001* *In favour of ice water submersion*	1, 14 vs 7 §	Armstrong, 1996
Cooling rate (°C/min), mean±SEM	1. Ice-water immersion 2. Cold-water immersion 3. Mock immersion	<u>Statistically significant:</u> Start immersion (SI) to 10 min: 0.16±0.02 vs 0.17±0.02 vs 0.11±0.01 no effect size/CI available p<0.05 (=significant for every time point thereafter) *In favour of ice-water and cold-water immersion*	1, 17 vs 17 vs 17 § (within subjects design)	Clements, 2002
Rate of rectal temperature reduction (°C/min)	1. Submersion of torso in cold water 2. Submersion of hands and feet in cold water 3. Sitting in the shade	<u>Statistically significant:</u> 1 vs 3: 0.25±0.10 vs 0.1±0.04 MD: 0.15, 95% CI[0.06; 0.24], p=0.002* *In favour of submersion of torso in cold water* 2 vs 3: 0.16±0.05 vs 0.10±0.04 MD: 0.06; 95% CI[0.00; 0.12], p=0.04* *In favour of submersion of hands and feet in cold water*	1, 5 vs 5 vs 5 § (within subjects design)	Clapp, 2001

Decrease in rectal temperature (°C)		After 10 min cooling: <u>Statistically significant:</u> 1 vs 3: 1.2±0.46 vs 0.42±0.14 MD: 0.78, 95%CI [0.36, 1.20], p=0.0003* *In favour of submersion of torso in cold water* Not statistically significant: 2 vs 3: 0.74±0.33 vs 0.42±0.14 MD: 0.32, 95%CI [0.01; 0.63], p=0.05 After 30 min cooling: <u>Statistically significant:</u> 1 vs 3: 0.63±0.41 and 0.14±0.14 MD: 0.49, 95%CI [0.11, 0.87], p=0.01* *In favour of submersion of torso in cold water* 2 vs 3: 0.45±0.30 vs 0.14±0.14 MD: 0.32, 95%CI [0.01; 0.63], p=0.04* *In favour of submersion of hands and feet in cold water*		
Rectal temperature (°C)	1. Ice-water immersion 2. Cold-water immersion 3. Mock immersion	<u>Statistically significant</u>: Greater rectal temperature for mock immersion than ice-water immersion at 12 minutes of immersion and 3, 6 and 15 minutes post-immersion p<0.05† *In favour of ice-water and cold-water immersion*	1, 17 §	Clements, 2002
Cooling time (min)	1. 6 ICPs 2. Body covered with ICPs 3. Evaporative cooling 4. Evaporative cooling + 6 ICPs 5. Passive cooling	<u>Statistically significant:</u> 2, 3, 4 vs 5: shorter cooling periods: p<0.05† *In favour of body covered with ICPs, evaporative cooling and evaporative cooling + 6 ice packs*	1, 5 §	Kielblock, 1986

Mean ± SD (unless otherwise indicated)

*Calculations done by the reviewer(s) using Review Manager software

† Imprecision (lack of data)

§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Armstrong, 1996	Unclear, not mentioned	Unclear, not mentioned, but irrelevant	No	No	
Clapp, 2001	Unclear, not mentioned	Unclear, not mentioned, but irrelevant	No	No	
Clements, 2002	Unclear, not mentioned how randomization was done	No, but irrelevant	No	No	

Kielblock, 1986	Unclear, not mentioned	Unclear, not mentioned, but irrelevant	No	No	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/lack of data/large variability of the results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is limited evidence in favour of cooling: It was shown that ice water submersion of the torso only, or hands and feet only or cold water submersion resulted in a statistically significant increase of cooling rate, compared to air exposure (Armstrong 1996, Clapp 2001, Clements 2002). It was shown that ice water submersion of the torso only or hands and feet only or cold water submersion resulted in a statistically significant decrease of rectal temperature, compared to sitting in the shade (Clapp 2001, Clements 2002). It was shown that a body covered with instant cold packs (ICPs) or evaporative cooling with or without ICPs resulted in a statistically significant decrease of cooling time, compared to cooling with 6 ICPs or passive cooling air exposure (Kielblock 1986). Evidence is of low quality and results cannot be considered precise due to limited sample size and lack of data.
Reference(s)	**Articles** Armstrong LE, Crago AE, Adams R, Roberts WO, Marsh CM. *Whole body cooling of hyperthermic runners: comparison of two field therapies*. Am J of Emerg Med 1996, 14(4):355-358 Clapp AJ, Bishop PA, Muir I, Walker JL. *Rapid cooling techniques in joggers experiencing heat strain*. J Sci Med Sport 2001, 4(2):160-167 Clements JM, Casa DJ, Knight JC, McClung JM, Blake AS, Meenen PM, Gilmer AM, Caldwell KA. *Ice-water immersion and cold-water immersion provide similar cooling rates in runners with exercise-induced hyperthermia.* J Athl Train 2002, 37(2):146-150 Kielblock AJ, Van Rensburg JP, Franz RM. *Body cooling as a method for reducing hyperthermia*. S Afr Med J 1986, 69:376-380 Newport M. *BestBET 3:In patients with heatstroke is whole-body ice-water immersion the best cooling method?* Emerg Med J 2012, 29(10):855-856 **Systematic reviews** Bouchama A, Dehbi M, Chaves-Carballo E. *Cooling and hemodynamic management in heatstroke: practical recommendations*. Critical Care 2007, 11:R54 Smith JE. *Cooling methods used in the treatment of exertional heat illness*. Br J Sports Med 2005, 39:503-207

Heat stroke – Reduction of activity (Risk Factor)

Question (PICO)	In people (P), is reduction of activity (RF) a protective factor for heatstroke (O) compared to not doing this (C)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "Heat Stroke"] OR "heat stroke":ti,ab OR "sun stroke":ti,ab OR heatstroke:ti,ab OR sunstroke:ti,ab

	MEDLINE (via PubMed interface) using the following search strategy: 1. "Heat Stroke"[Mesh] OR "heat stroke"[TIAB] OR "sun stroke"[TIAB] OR heatstroke[TIAB] OR sunstroke[TIAB] 2. Exercis*[TIAB] OR activit* [TIAB] 3. Drink*[TIAB] OR liquids[TIAB] OR water[TIAB] 4. Shower*[TIAB] OR bath*[TIAB] 5. Ventilat* OR fan[TIAB] OR air-conditioning[TIAB] OR cool*[TIAB] 6. 2-5 OR 7. "Risk factors"[Mesh] OR Risk factor*[TIAB] OR protective factor*[TIAB] OR prognostic factor*[TIAB] 8. 1 AND 6 AND 7 **Embase** (via Embase.com interface) using the following search strategy: 1. 'heat stroke'/exp OR 'heat stroke':ab,ti OR 'sun stroke':ab,ti OR heatstroke:ab,ti OR sunstroke:ab,ti 2. Exercis*:ab,ti OR activit*:ab,ti 3. Drink*:ab,ti OR liquids:ab,ti OR water:ab,ti 4. Shower*:ab,ti OR bath*:ab,ti 5. Ventilat*:ab,ti OR fan:ab,ti OR air-conditioning:ab,ti OR cool*:ab,ti 6. 2-5 OR 7. 'risk factor'/exp OR (Risk NEXT/1 factor*):ab,ti OR (Protective NEXT/1 factor*):ab,ti OR (Prognostic NEXT/1 factor*):ab,ti 8. 1 AND 6 AND 7 Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	11 September 2015
In/Exclusion criteria	**Population**: Include: adults or children **Intervention**: Include: use of a fan/air conditioning/ventilation, visit to air conditioned rooms **Outcome**: Include: risk of heat stroke, risk of death during heat wave **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Risk factor	Remarks
Kilbourne, 1982, USA	Observational study: case-control study	Cases: 156 persons with heatstroke (severe heat illness with documented hyperthermia) Controls: 462 control subjects matched by age, sex, and neighbourhood of residence	Multiple risk factors [only data on reduction of activity were extracted]	A multivariate logistic regression model was used.

Synthesis of findings

Outcome	Risk factor	Effect Size	#studies, # participants	Reference
Relative risk of heatstroke	Reduction of activity	Statistically significant: RR:0.19, 95%CI [0.08;0.43] (p<0.05) £† *With benefit for reduction of activity*	1, 156 vs 462	Kilbourne, 1982

£ No raw data available

† Imprecision (lack of data)

Quality of evidence

Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations
Kilbourne, 1982	No (matched cases and controls)	No	No (multivariable analysis)	No	

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Lack of data
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Conclusion	There is limited evidence with benefit for reduction of activity. It was shown that reduction of activity resulted in a statistically significant decreased risk of all-causes deaths during heath waves (Kilbourne 1982). Evidence is of very low quality and results cannot be considered precise due to lack of data.
Reference(s)	**Articles** Kilbourne EM, Choi K, Jones TS, Thacker SB. *Risk factors for heatstroke. A case-control study*. JAMA 1982, 247(24):3332-6

Heat stroke – Drinking (Risk Factor)

Question (PICO)	In people (P), is drinking more frequently (RF) a protective factor for heatstroke (O) compared to not doing this (C)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "Heat Stroke"] OR "heat stroke":ti,ab OR "sun stroke":ti,ab OR heatstroke:ti,ab OR sunstroke:ti,ab **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Heat Stroke"[Mesh] OR "heat stroke"[TIAB] OR "sun stroke"[TIAB] OR heatstroke[TIAB] OR sunstroke[TIAB] 2. Exercis*[TIAB] OR activit* [TIAB] 3. Drink*[TIAB] OR liquids[TIAB] OR water[TIAB] 4. Shower*[TIAB] OR bath*[TIAB] 5. Ventilat* OR fan[TIAB] OR air-conditioning[TIAB] OR cool*[TIAB] 6. 2-5 OR

	7. "Risk factors"[Mesh] OR Risk factor*[TIAB] OR protective factor*[TIAB] OR prognostic factor*[TIAB] 8. 1 AND 6 AND 7 **Embase** (via Embase.com interface) using the following search strategy: 1. 'heat stroke'/exp OR 'heat stroke':ab,ti OR 'sun stroke':ab,ti OR heatstroke:ab,ti OR sunstroke:ab,ti 2. Exercis*:ab,ti OR activit*:ab,ti 3. Drink*:ab,ti OR liquids:ab,ti OR water:ab,ti 4. Shower*:ab,ti OR bath*:ab,ti 5. Ventilat*:ab,ti OR fan:ab,ti OR air-conditioning:ab,ti OR cool*:ab,ti 6. 2-5 OR 7. 'risk factor'/exp OR (Risk NEXT/1 factor*):ab,ti OR (Protective NEXT/1 factor*):ab,ti OR (Prognostic NEXT/1 factor*):ab,ti 8. 1 AND 6 AND 7 Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	11 September 2015
In/Exclusion criteria	**Population**: Include: adults or children **Intervention**: Include: drinking more frequently (water, other fluids) **Outcome**: Include: risk of heat stroke, risk of death during heat wave **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Risk factor	Remarks
Kilbourne, 1982, USA	Observational study: case-control study	Cases: 156 persons with heatstroke (severe heat illness with documented hyperthermia) Controls: 462 control subjects matched by age, sex, and neighbourhood of residence	Multiple risk factors [only data on taking extra liquids were extracted]	A multivariate logistic regression model was used.

Synthesis of findings

Outcome	Risk factor	Effect Size	#studies, # participants	Reference
Relative risk of heatstroke	Taking extra liquids	Statistically significant: RR:0.27, 95%CI [0.11;0.66] (p<0.05) £† *With benefit for taking extra liquids*	1, 156 vs 462	Kilbourne, 1982

£ No raw data available

† Imprecision (lack of data)

Quality of evidence

Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations
Kilbourne, 1982	No (matched cases and controls)	No	No (multivariable analysis)	No	

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Lack of data
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Conclusion	There is limited evidence in favour of taking extra liquids. It was shown that taking extra liquids compared to not doing this resulted in a statistically significant decreased risk of all-causes deaths during heath waves (Kilbourne 1982). Evidence is of very low quality and results cannot be considered precise due to lack of data.
Reference(s)	**Articles** Kilbourne EM, Choi K, Jones TS, Thacker SB. *Risk factors for heatstroke. A case-control study*. JAMA 1982, 247(24):3332-6

Heat stroke – Fan/air conditioning (Risk Factor)

Question (PICO)	In people (P), is using a fan or air conditioning (RF) a protective factor for heatstroke (O) compared to not doing this (C)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "Heat Stroke"] OR "heat stroke":ti,ab OR "sun stroke":ti,ab OR heatstroke:ti,ab OR sunstroke:ti,ab **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Heat Stroke"[Mesh] OR "heat stroke"[TIAB] OR "sun stroke"[TIAB] OR heatstroke[TIAB] OR sunstroke[TIAB] 2. Exercis*[TIAB] OR activit* [TIAB] 3. Drink*[TIAB] OR liquids[TIAB] OR water[TIAB] 4. Shower*[TIAB] OR bath*[TIAB] 5. Ventilat* OR fan[TIAB] OR air-conditioning[TIAB] OR cool*[TIAB] 6. 2-5 OR 7. "Risk factors"[Mesh] OR Risk factor*[TIAB] OR protective factor*[TIAB] OR prognostic factor*[TIAB] 8. 1 AND 6 AND 7 **Embase** (via Embase.com interface) using the following search strategy: 1. 'heat stroke'/exp OR 'heat stroke':ab,ti OR 'sun stroke':ab,ti OR heatstroke:ab,ti OR sunstroke:ab,ti 2. Exercis*:ab,ti OR activit*:ab,ti 3. Drink*:ab,ti OR liquids:ab,ti OR water:ab,ti 4. Shower*:ab,ti OR bath*:ab,ti

	5. Ventilat*:ab,ti OR fan:ab,ti OR air-conditioning:ab,ti OR cool*:ab,ti 6. 2-5 OR 7. 'risk factor'/exp OR (Risk NEXT/1 factor*):ab,ti OR (Protective NEXT/1 factor*):ab,ti OR (Prognostic NEXT/1 factor*):ab,ti 8. 1 AND 6 AND 7 Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	11 September 2015
In/Exclusion criteria	**Population**: Include: adults or children **Intervention**: Include: use of a fan/air conditioning/ventilation, visit to air conditioned rooms **Outcome**: Include: risk of heat stroke, risk of death during heat wave **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Risk factor	Remarks
Bouchama, 2007, Saoudi Arabia	Systematic review	6 observational studies (case-control studies) involving 1065 heat wave–related deaths	Multiple risk factors [only data concerning use of a fan or air conditioning were extracted]	
Vandentorren, 2006, France	Observational study: case-control study	Cases: 315 persons aged 65 and over who died during a heat wave in France Controls: 282 persons who did not die during the same heat wave, matched for age, sex, and residential area; randomly selected from telephone records	Multiple risk factors [only data concerning use of a fan or air conditioning were extracted]	A multivariate analysis was used.

Synthesis of findings

Outcome	Risk factor	Effect Size	#studies, # participants	Reference
Risk of all-causes deaths during heath waves	Has working home air conditioning	Statistically significant: OR: 0.23, 95%CI [0.1;0.6] ($p<0.05$) £† *With benefit for a working home air conditioning*	6, 1157 vs 1485	Bouchama, 2007
	Has working fan	Not statistically significant:	3, 394 vs 425	

		OR: 0.60, 95%CI [0.4;1.1] ¥ (p>0.05) £†		
	Used cooling device or techniques	Statistically significant: OR: 0.32, 95%CI [0.12;0.82] (p<0.05) £† *With benefit for using a cooling device*	1, 315 vs 282	Vandentorren, 2006
	Visited cooler places vs not	Not statistically significant: OR: 0.46, 95%CI [0.15;1.47] ¥ (p>0.05) £†	1, 315 vs 282	
	Visited other air-conditioned places	Statistically significant: OR: 0.34, 95%CI [0.2;0.5] (p<0.05) £† *With benefit for visiting other air conditioned places*	5, 843 vs 1171	Bouchama, 2007

£ No raw data available

† Imprecision (lack of data)

¥ Imprecision (large variability of results)

Quality of evidence

Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations
Kilbourne, 1982	No (matched cases and controls)	No	No (multivariable analysis)	No	
Vandentorren, 2006	No (matched cases and controls)	No	No (multivariable analysis)	No	

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	0	See systematic review (Bouchama 2007) and table 'Quality of evidence'
Imprecision	-1	Lack of data, large variability of the results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Conclusion	It was shown that the following risk factors resulted in a statistically significant decreased risk of all-causes deaths during heath waves: having a working home air-conditioning (vs not), using a cooling device or techniques (vs not) or visiting other air-conditioned places (vs not) (Bouchama 2007, Vandentorren 2006). A statistically significant decreased risk of all-causes deaths during heath waves in case/presence of having a working fan or visiting cooler places could not be demonstrated (Bouchama 2007, Vandentorren 2006). Evidence is of very low quality and results cannot be considered precise due to lack of data and large variability of results.
Reference(s)	**Articles** Bouchama A, Dehbi M, Mohamed G, Matthies F, Shoukri M, Menne B. *Prognostic factors in heat wave related deaths: a meta-analysis*. Arch Intern Med 2007, 167(20):2170-6 Vandentorren S, Bretin P, Zeghnoun A, Mandereau-Bruno L, Croisier A, Cochet C, Ribéron J, Siberan I, Declercq B, Ledrans M. *August 2003 heat wave in France: risk factors for death of elderly people living at home*. Eur J Public Health 2006, 16(6):583-91

Heat stroke – Showers (Risk Factor)

Question (PICO)	In people (P), is taking extra showers (RF) a protective factor for heatstroke (O) compared to not doing this (C)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "Heat Stroke"] OR "heat stroke":ti,ab OR "sun stroke":ti,ab OR heatstroke:ti,ab OR sunstroke:ti,ab **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Heat Stroke"[Mesh] OR "heat stroke"[TIAB] OR "sun stroke"[TIAB] OR heatstroke[TIAB] OR sunstroke[TIAB] 2. Exercis*[TIAB] OR activit* [TIAB] 3. Drink*[TIAB] OR liquids[TIAB] OR water[TIAB] 4. Shower*[TIAB] OR bath*[TIAB] 5. Ventilat* OR fan[TIAB] OR air-conditioning[TIAB] OR cool*[TIAB] 6. 2-5 OR 7. "Risk factors"[Mesh] OR Risk factor*[TIAB] OR protective factor*[TIAB] OR prognostic factor*[TIAB] 8. 1 AND 6 AND 7 **Embase** (via Embase.com interface) using the following search strategy: 1. 'heat stroke'/exp OR 'heat stroke':ab,ti OR 'sun stroke':ab,ti OR heatstroke:ab,ti OR sunstroke:ab,ti 2. Exercis*:ab,ti OR activit*:ab,ti 3. Drink*:ab,ti OR liquids:ab,ti OR water:ab,ti 4. Shower*:ab,ti OR bath*:ab,ti 5. Ventilat*:ab,ti OR fan:ab,ti OR air-conditioning:ab,ti OR cool*:ab,ti 6. 2-5 OR 7. 'risk factor'/exp OR (Risk NEXT/1 factor*):ab,ti OR (Protective NEXT/1 factor*):ab,ti OR (Prognostic NEXT/1 factor*):ab,ti 8. 1 AND 6 AND 7 Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	11 September 2015
In/Exclusion criteria	**Population**: Include: adults or children. **Intervention**: Include: taking extra showers **Outcome**: Include: risk of heat stroke, risk of death during heat wave **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Risk factor	Remarks
Bouchama, 2007, Saoudi Arabia	Systematic review	6 observational studies (case-control studies) involving 1065 heat wave–related deaths	Multiple risk factors [only data on taking extra showers was extracted]	

Synthesis of findings

Outcome	Risk factor	Effect Size	#studies, # participants	Reference
Risk of all-causes deaths during heath waves	Takes extra showers	Not statistically significant: OR: 0.32, 95%CI [0.1;1.1] ¥ (p>0.05) £†	3, 636 vs 650	Bouchama, 2007

£ No raw data available

† Imprecision (lack of data)

¥ Imprecision (large variability of results)

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	0	See systematic review (Bouchama 2007)
Imprecision	-1	Lack of data, large variability of the results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Conclusion	There is limited evidence neither for the benefit/harm of taking extra showers. A statistically significant decreased risk of all-causes deaths during heath waves in case of taking extra showers compared to not doing this could not be demonstrated (Bouchama 2007). Evidence is of very low quality and results of this study are imprecise due to lack of data and large variability of results.
Reference(s)	**Systematic reviews** Bouchama A, Dehbi M, Mohamed G, Matthies F, Shoukri M, Menne B. *Prognostic factors in heat wave related deaths: a meta-analysis*. Arch Intern Med 2007, 167(20):2170-6

Heat stroke – Special clothing (Risk Factor)

Question (PICO)	In people (P), is using special clothing (RF) a protective factor for heatstroke (O) compared to not doing this (C)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "Heat Stroke"] OR "heat stroke":ti,ab OR "sun stroke":ti,ab OR heatstroke:ti,ab OR sunstroke:ti,ab **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Heat Stroke"[Mesh] OR "heat stroke"[TIAB] OR "sun stroke"[TIAB] OR heatstroke[TIAB] OR sunstroke[TIAB] 2. Exercis*[TIAB] OR activit* [TIAB] 3. Drink*[TIAB] OR liquids[TIAB] OR water[TIAB] 4. Shower*[TIAB] OR bath*[TIAB] 5. Ventilat* OR fan[TIAB] OR air-conditioning[TIAB] OR cool*[TIAB] 6. 2-5 OR

	7. "Risk factors"[Mesh] OR Risk factor*[TIAB] OR protective factor*[TIAB] OR prognostic factor*[TIAB] 8. 1 AND 6 AND 7 **Embase** (via Embase.com interface) using the following search strategy: 1. 'heat stroke'/exp OR 'heat stroke':ab,ti OR 'sun stroke':ab,ti OR heatstroke:ab,ti OR sunstroke:ab,ti 2. Exercis*:ab,ti OR activit*:ab,ti 3. Drink*:ab,ti OR liquids:ab,ti OR water:ab,ti 4. Shower*:ab,ti OR bath*:ab,ti 5. Ventilat*:ab,ti OR fan:ab,ti OR air-conditioning:ab,ti OR cool*:ab,ti 6. 2-5 OR 7. 'risk factor'/exp OR (Risk NEXT/1 factor*):ab,ti OR (Protective NEXT/1 factor*):ab,ti OR (Prognostic NEXT/1 factor*):ab,ti 8. 1 AND 6 AND 7 Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	11 September 2015
In/Exclusion criteria	**Population**: Include: adults or children **Intervention**: Include: wearing special clothing, such as thin or light clothes **Outcome**: Include: risk of heat stroke, risk of death during heat wave **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Risk factor	Remarks
Vandentorren, 2006, France	Observational study: case-control study	Cases: 315 persons aged 65 and over who died during a heat wave in France Controls: 282 persons who did not die during the same heat wave, matched for age, sex, and residential area; randomly selected from telephone records	Multiple risk factors [only data concerning special clothing were extracted]	A multivariate analysis was used.

Synthesis of findings

Outcome	Risk factor	Effect Size	#studies, # participants	Reference
Risk of all-causes deaths during heath waves	Dressed lightly vs not	Statistically significant: OR: 0.22, 95%CI [0.09;0.55] ($p<0.05$) £† *With benefit for dressing lightly*	1, 315 vs 282	Vandentorren, 2006

£ No raw data available
† Imprecision (lack of data)

Quality of evidence

Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations
Vandentorren, 2006	No (matched cases and controls)	No	No (multivariable analysis)	No	

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Lack of data
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Conclusion	There is limited evidence with benefit for dressing lightly. It was shown that dressing lightly compared to not doing this resulted in a statistically significant decreased risk of all-causes deaths during heath waves (Vandentorren 2006). Evidence is of very low quality and results cannot be considered precise due to lack of data.
Reference(s)	**Articles** Vandentorren S, Bretin P, Zeghnoun A, Mandereau-Bruno L, Croisier A, Cochet C, Ribéron J, Siberan I, Declercq B, Ledrans M. *August 2003 heat wave in France: risk factors for death of elderly people living at home*. Eur J Public Health 2006, 16(6):583-91

Heat stroke – Social contact (Risk Factor)

Question (PICO)	In people (P), is increased social contact (RF) a protective factor for heatstroke (O) compared to not doing this (C)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "Heat Stroke"] OR "heat stroke":ti,ab OR "sun stroke":ti,ab OR heatstroke:ti,ab OR sunstroke:ti,ab **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Heat Stroke"[Mesh] OR "heat stroke"[TIAB] OR "sun stroke"[TIAB] OR heatstroke[TIAB] OR sunstroke[TIAB] 2. Exercis*[TIAB] OR activit* [TIAB] 3. Drink*[TIAB] OR liquids[TIAB] OR water[TIAB] 4. Shower*[TIAB] OR bath*[TIAB] 5. Ventilat* OR fan[TIAB] OR air-conditioning[TIAB] OR cool*[TIAB] 6. 2-5 OR 7. "Risk factors"[Mesh] OR Risk factor*[TIAB] OR protective factor*[TIAB] OR prognostic factor*[TIAB] 8. 1 AND 6 AND 7 **Embase** (via Embase.com interface) using the following search strategy:

	1. 'heat stroke'/exp OR 'heat stroke':ab,ti OR 'sun stroke':ab,ti OR heatstroke:ab,ti OR sunstroke:ab,ti 2. Exercis*:ab,ti OR activit*:ab,ti 3. Drink*:ab,ti OR liquids:ab,ti OR water:ab,ti 4. Shower*:ab,ti OR bath*:ab,ti 5. Ventilat*:ab,ti OR fan:ab,ti OR air-conditioning:ab,ti OR cool*:ab,ti 6. 2-5 OR 7. 'risk factor'/exp OR (Risk NEXT/1 factor*):ab,ti OR (Protective NEXT/1 factor*):ab,ti OR (Prognostic NEXT/1 factor*):ab,ti Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	11 September 2015
In/Exclusion criteria	**Population**: Include: adults or children **Intervention**: Include: increased social contact **Outcome**: Include: risk of heat stroke, risk of death during heat wave **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Risk factor	Remarks
Bouchama, 2007, Saoudi Arabia	Systematic review	6 observational studies (case-control studies) involving 1065 heat wave–related deaths	Multiple risk factors [only data on increased social contact were extracted]	

Synthesis of findings

Outcome	Risk factor	Effect Size	#studies, # participants	Reference
Risk of all-causes deaths during heath waves	Increased social contact	Statistically significant: OR: 0.40, 95%CI [0.2;0.8] (p<0.05) £† *With benefit for increased social contact*	4, 975 vs 989	Bouchama, 2007

£ No raw data available

† Imprecision (lack of data)

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	0	See systematic review (Bouchama 2007)
Imprecision	-1	Lack of data
Inconsistency	0	
Indirectness	0	

Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Conclusion	There is limited evidence with benefit for increased social contact. It was shown that increased social contact resulted in a statistically significant decreased risk of all-causes deaths during heath waves (Bouchama 2007). Evidence is of very low quality and results cannot be considered precise due to lack of data.
Reference(s)	**Articles** Bouchama A, Dehbi M, Mohamed G, Matthies F, Shoukri M, Menne B. *Prognostic factors in heat wave related deaths: a meta-analysis*. Arch Intern Med 2007, 167(20):2170-6

Sweat rash – Cooling or showering (First Aid)

Question (PICO)	In humans with sweat rash (P), is cooling or showering (I) compared to not doing this (C) effective to change functional recovery, complications, time to resumption of usual activities, restoration to the pre-exposure condition, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "Miliaria"] OR "prickly heat":ti,ab OR ((sweat*:ti,ab OR heat:ti,ab) AND rash:ti,ab) **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Miliaria"[Mesh] OR miliaria[TIAB] OR "sweat gland disease"[TIAB] OR ((sweat*[TIAB] OR heat[TIAB]) AND rash[TIAB]) OR "prickly heat"[TIAB] 2. "Cold Temperature"[Mesh] OR "Cryotherapy"[Mesh] OR "Ice"[Mesh] OR shower*[TIAB] OR cold[TIAB] OR cool*[TIAB] OR ice[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'sweat gland disease'/exp OR miliaria:ab,ti OR 'sweat gland disease':ab,ti OR ((sweat*:ab,ti OR heat:ab,ti) AND rash:ab,ti) OR 'prickly heat':ab,ti 2. 'cold'/exp OR 'cryotherapy'/exp OR 'ice'/exp OR shower*:ab,ti OR cold:ab,ti OR cool*:ab,ti OR ice:ab,ti 3. 1-2 AND
Search date	9 September 2015
In/Exclusion criteria	**Population**: Include: people with sweat rash **Intervention**: Include: cooling or showering **Outcome**: Include: disappearance of rash, functional recovery, complications, time to resumption of usual activities, restoration to the pre-exposure condition, time to resolution of symptoms **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline)

	Publication year: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion(s)	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

ELECTRICAL INJURIES AND LIGHNING INJURY

Electrical injuries and lightning injury – Various risk factors (Risk Factor)

Question (PICO)	In people (P) which risk factors exist (I) for electrical injuries and lightning injury (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "Electric injuries"] OR lightning:ti,ab OR (electric NEXT injur*):ti,ab OR (electrical NEXT injur*):ti,ab OR (electric NEXT burn*):ti,ab (electrical NEXT burn*):ti,ab **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Electric Injuries"[Mesh] OR lightning[TIAB] OR electric injur*[TIAB] OR electrical injur*[TIAB] OR electric burn*[TIAB] OR electrical burn*[TIAB] 2. "Risk factors"[Mesh] OR risk factor*[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'electric injury'/exp OR lightning:ab,ti OR (electric NEXT/1 injur*):ab,ti OR (electrical NEXT/1 injur*):ab,ti OR (electric NEXT/1 burn*):ab,ti (electrical NEXT/1 burn*):ab,ti 2. 'risk factor'/exp OR (risk NEXT/1 factor*):ab,ti 3. 1-2 AND
Search date	8 September 2015
In/Exclusion criteria	**Population**: Include: adults or children **Intervention**: Include: modifiable, proximal risk factor with a potential immediate implication for practice that results in primary prevention at the household or community level. Risk factors related to healthy persons. Exclude: risk factors that lead to interventions with already proven effectiveness. The risk factor that does not precede the outcome. The risk factor is common sense. **Outcome**: Include: prevention of CO poisoning **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion(s)	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

ACCIDENTS IN THE WATER

Drowning – Removing the victim horizontally (First Aid)

Question (PICO)	In humans who are drowning (P) is removing the victim horizontally (I) compared to not doing this (C) effective to prevent a drop in blood pressure/health problems (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh drowning] OR [mh "near drowning"] OR drown*:ti,ab,kw **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. drowning[Mesh] OR "near drowning"[Mesh] OR drown*[TIAB] 2. posture[Mesh] OR position*[TIAB] OR horizontal*[TIAB] OR posture[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. drowning/exp OR 'near drowning'/exp OR drown*:ab,ti 2. 'body position'/exp OR posture:ab,ti OR position*:ab,ti OR horizontal*:ab,ti 3. 1-2 AND
Search date	15 September 2015
In/Exclusion criteria	**Population**: People who are drowning. **Intervention**: removing the victim horizontally. **Comparison**: removing the victim in another position. **Outcome**: drop in blood pressure, health problems. **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Hypothermia – Hot drink (First Aid)

Question (PICO)	In humans with hypothermia (P), is drinking a hot drink (I) compared to not doing this (C) effective to prevent further hypothermia (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh hypothermia] OR hypothermia:ti,ab,kw OR [mh "body temperature"] OR "body temperature":ti,ab,kw 2. (hot:ti,ab,kw OR warm:ti,ab,kw) AND drink*:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. hypothermia[Mesh] OR hypothermia[TIAB] OR "body temperature"[Mesh] OR "body temperature"[TIAB] 2. (hot[TIAB] OR warm[TIAB]) AND drink*[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. hypothermia/exp OR 'accidental hypothermia'/exp OR hypothermia:ab,ti OR 'body temperature'/exp OR 'body temperature':ab,ti 2. (hot:ab,ti OR warm:ab,ti) AND drink*:ab,ti 3. 1-2 AND
Search date	16 September 2015
In/Exclusion criteria	**Population**: people with hypothermia **Intervention**: drinking a hot or warm drink **Comparison**: Not drinking or drinking a cold drink or a drink at room temperature. **Outcome**: reduction of hypothermia, prevention of further hypothermia **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Drowning – Flotation device (Risk factor)

Question (PICO)	In humans (P) is using a flotation device (RF) a protective factor for drowning (O) compared to not using a flotation device (C)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh drowning] OR [mh "near drowning"] OR drown*:ti,ab,kw **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. drowning[Mesh] OR "near drowning"[Mesh] OR drown*[TIAB] 2. "risk factors"[Mesh] OR risk*[TIAB] OR prevent*[TIAB] 3. fenc*[TIAB] OR barrier*[TIAB] OR supervis*[TIAB] OR unsupervis*[TIAB] OR guard*[TIAB] OR ice[TIAB] OR float*[TIAB] OR flot*[TIAB] OR overestimat*[TIAB] OR alone[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. drowning/exp OR 'near drowning'/exp OR drown*:ab,ti 2. 'risk factor'/exp OR risk*:ab,ti OR prevent*:ab,ti 3. fenc*:ab,ti OR barrier*:ab,ti OR supervis*:ab,ti OR unsupervis*:ab,ti OR guard*:ab,ti OR ice:ab,ti OR float*:ab,ti OR flot*:ab,ti OR overestimat*:ab,ti OR alone:ab,ti 4. 1-3 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	17 September 2015
In/Exclusion criteria	**Population**: Include: Healthy people of all ages. Exclude: people with medical conditions such as epilepsy. **Risk factor**: Include: not using a flotation device. Exclude: educational programmes. **Comparison**: Include: using a flotation device. **Outcome**: Include: Drowning or near-drowning **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Risk factor	Remarks
Yang, 2007, Australia	Observational: case-control study	11 districts in a costal township and 9 districts in an inland township in the GuangXi Province in China.	Several risk factors	

		Drowning cases (between 1-14 years) were searched in the database of the registry of deaths held by the local Birth Planning Committee. All cases registered between January 2002 and December 2004 were registered. Controls were recruited by randomly selecting households in the districts adjacent to where each case lived, until 2 children from different households had been identified. 133 cases and 266 controls were selected.	[only data on flotation devices were extracted]	

Synthesis of findings

Outcome	Risk factor	Effect Size	#studies, # participants	Reference
Drowning	no flotation device (children aged 1-14 years) vs flotation device	Not statistically significant: 122/133 vs 226/266 § OR: 2.3, 95%CI [0.97; 3.96] (p=0.056)	1, 64 vs 128	Yang, 2007
	no flotation device (children aged 1-4 years) vs flotation device	Statistically significant: 62/64 vs 113/128 § aOR: 2.3, 95%CI [1.4; 4.5] (p=0.027) *With harm for no flotation device*	1, 64 vs 128	

§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations
Yang, 2007	No, controls were matched precisely for age and gender and were selected from an adjacent district	Yes, possible recall bias	No, multivariate analysis was performed	No	

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited number of events
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Conclusion	There is limited evidence with benefit for flotation devices. It was shown that the use of flotation devices resulted in a statistically significant decreased risk of drowning in children aged 1-4 years, compared to not using flotation devices (Yang 2007). A statistically significant increased risk of drowning when not using flotation devices compared to using flotation devices in children aged 1-14 years could not be demonstrated (Yang 2007). Evidence is of very low quality and results cannot be considered precise due to limited number of events.
Reference(s)	**Articles** Yang L, Nong Q-Q, Li C-L, Fen Q-M, Lo SK. *Risk factors for childhood drowning in rural regions of a developing country: a case-control study*. Injury Prevention 2007, 13:178-182

Drowning – Pool fencing (Risk Factor)

Question (PICO)	In humans (P) is a fence around a pool (RF) a protective factor for drowning (O) compared to no pool fencing (C)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh drowning] OR [mh "near drowning"] OR drown*:ti,ab,kw **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. drowning[Mesh] OR "near drowning"[Mesh] OR drown*[TIAB] 2. "risk factors"[Mesh] OR risk*[TIAB] OR prevent*[TIAB] 3. fenc*[TIAB] OR barrier*[TIAB] OR supervis*[TIAB] OR unsupervis*[TIAB] OR guard*[TIAB] OR ice[TIAB] OR float*[TIAB] OR flot*[TIAB] OR overestimat*[TIAB] OR alone[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. drowning/exp OR 'near drowning'/exp OR drown*:ab,ti 2. 'risk factor'/exp OR risk*:ab,ti OR prevent*:ab,ti 3. fenc*:ab,ti OR barrier*:ab,ti OR supervis*:ab,ti OR unsupervis*:ab,ti OR guard*:ab,ti OR ice:ab,ti OR float*:ab,ti OR flot*:ab,ti OR overestimat*:ab,ti OR alone:ab,ti 4. 1-3 AND Cochrane review: Thompson, 1998 (this review was considered as stable in 2010), therefore no update of this review was done.
Search date	17 September 2015
In/Exclusion criteria	**Population**: Include: Healthy people of all ages. Exclude: people with medical conditions such as epilepsy. **Intervention**: Include: pool fencing. **Comparison**: Include: no pool fencing. **Outcome**: Include: Prevention of drowning or near-drowning **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Risk factor	Remarks
Thompson, 1998	Systematic review	3 population-based case-control studies including children who drowned or	Fenced vs unfenced pools	This review was considered as stable in 2010.

		were treated for an immersion injury.		Isolation fencing: a fence or building wall restricts access to the pool. All ancillary structures excluded from the pool area and a maximum distance between pool fence and edge of pool is described. Perimeter fencing: the boundary of the house allotment has a fence restricting access to the property by a toddler but there is no restriction of physical access for toddlers from the house to the pool.

Synthesis of findings

Outcome	Risk factor	Effect Size	#studies, # participants	Reference
Drowning and near-drowning	Fencing vs no fencing (all pool types)	Statistically significant: 25/72 vs 136/204 § OR: 0.27, 95%CI [0.15; 0.47] (p<0.00001) *In favour of fencing*	1, 72 vs 204	Thompson, 1998
		Statistically significant: 20/100 vs 46/100 § OR: 0.29, 95%CI [0.16; 0.55] (p=0.00013) *In favour of fencing*	1, 100 vs 100	
	Fencing vs no fencing (in-ground pools)	Statistically significant: 22/55 vs 93/127 § OR: 0.24, 95%CI [0.13; 0.48] (p=0.000034) *In favour of fencing*	1, 55 vs 127	
	Fencing vs no fencing (above ground pools)	Statistically significant: 3/13 vs 40/71 § OR: 0.23, 95%CI [0.06; 0.92] (p=0.037) *In favour of fencing*	1, 13 vs 71	
	Isolation vs perimeter fencing	Statistically significant: 9/27 vs 38/50 § OR: 0.16, 95%CI [0.06; 0.44] (p=0.00045) *In favour of isolation fencing*	1, 27 vs 50	

§ Imprecision (low number of events)

Quality of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	-1	See systematic review of Thompson 1998
Imprecision	-1	Limited number of events
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Conclusion	There is limited evidence in favour of pool fencing. It was shown that pool fencing resulted in a statistically significant decreased risk of drowning or near drowning, compared to no pool fencing (Thompson 1998). Evidence is of very low quality and results cannot be considered precise due to limited number of events.
Reference(s)	**Systematic reviews** Thompson DC, Rivara F. *Pool fencing for preventing drowning of children*. Cochrane Database of Systematic Reviews 1998, Issue 1. Art. No.: CD001047

Drowning – Adult supervision (Risk Factor)

Question (PICO)	In children (P) is the absence of adult supervision (RF) a risk factor for drowning (O) compared to the presence of adult supervision (C)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh drowning] OR [mh "near drowning"] OR drown*:ti,ab,kw **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. drowning[Mesh] OR "near drowning"[Mesh] OR drown*[TIAB] 2. "risk factors"[Mesh] OR risk*[TIAB] OR prevent*[TIAB] 3. fenc*[TIAB] OR barrier*[TIAB] OR supervis*[TIAB] OR unsupervis*[TIAB] OR guard*[TIAB] OR ice[TIAB] OR float*[TIAB] OR flot*[TIAB] OR overestimat*[TIAB] OR alone[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. drowning/exp OR 'near drowning'/exp OR drown*:ab,ti 2. 'risk factor'/exp OR risk*:ab,ti OR prevent*:ab,ti 3. fenc*:ab,ti OR barrier*:ab,ti OR supervis*:ab,ti OR unsupervis*:ab,ti OR guard*:ab,ti OR ice:ab,ti OR float*:ab,ti OR flot*:ab,ti OR overestimat*:ab,ti OR alone:ab,ti 4. 1-3 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	17 September 2015
In/Exclusion criteria	**Population**: Include: children Exclude: people with medical conditions such as epilepsy. **Risk factor**: Include: absence of adult supervision. Exclude: educational programmes. **Comparison**: Include: presence of adult supervision. **Outcome**: Include: Drowning or near-drowning **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values.

	Language: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Risk factor	Remarks
Yang, 2007, Australia	Observational: case-control study	11 districts in a costal township and 9 districts in an inland township in the GuangXi Province in China. Drowning cases (between 1-14 years) were searched in the database of the registry of deaths held by the local Birth Planning Committee. All cases registered between January 2002 and December 2004 were registered. Controls were recruited by randomly selecting households in the districts adjacent to where each case lived, until 2 children from different households had been identified. 133 cases and 266 controls were selected.	Several risk factors [only data on adult supervision were extracted]	

Synthesis of findings

Outcome	Risk factor	Effect Size	#studies, # participants	Reference
Drowning	no adult supervision (children aged 1-14 years)	Statistically significant: 56/133 vs 57/266 § OR: 2.67, 95%CI [1.70; 4.19] (p<0.0001)* *With harm for no adult supervision*	1, 133 vs 266	Yang, 2007
	no adult supervision (children aged 5-14 years)	Statistically significant: 42/64 vs 35/128 § aOR: 1.9, 95%CI [1.3; 5.6] (p=0.033) *With harm for no adult supervision*	1, 64 vs 128	

* Calculations done by the reviewer using Review Manager Software
§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations
Yang, 2007	No, controls were matched precisely for age and gender and were selected from an adjacent district	Yes, possible recall bias	No, multivariate analysis was performed	No	

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited number of events
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Conclusion	There is limited evidence with harm for the absence of adult supervision. It was shown that the absence of adult supervision resulted in a statistically significant increased risk of drowning, compared to the presence of adult supervision (Yang 2007). Evidence is of very low quality and results cannot be considered precise due to limited number of events.
Reference(s)	**Articles** Yang L, Nong Q-Q, Li C-L, Fen Q-M, Lo SK. *Risk factors for childhood drowning in rural regions of a developing country: a case-control study.* Injury Prevention 2007, 13:178-182

Decompression illness – Drinking (Prevention)

Question (PICO)	In humans (P), is drinking (1 L of) sports drink before diving (I) compared to not doing this (C) effective to prevent a decompression accident (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Decompression sickness"] OR decompression:ti,ab,kw OR "caisson disease":ti,ab,kw OR [mh "embolism, air"] OR embolism:ti,ab,kw 2. [mh Diving] OR diving:ti,ab,kw 3. [mh Exercise] OR exercise:ti,ab,kw OR [mh Drinking] OR drink*:ti,ab,kw 4. 1-3 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Decompression sickness"[Mesh] OR decompression[TIAB] OR "caisson disease"[TIAB] OR "embolism, air"[Mesh] OR embolism[TIAB] 2. Diving[Mesh] OR diving[TIAB] 3. Exercise[Mesh] OR exercise[TIAB] OR Drinking[Mesh] OR drink*[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'decompression sickness'/exp OR decompression:ab,ti OR 'caisson disease':ab,ti OR 'air embolism'/exp OR embolism:ab,ti 2. diving/exp OR diving:ab,ti 3. exercise/exp OR exercise:ab,ti OR drinking/exp OR drinking:ab,ti 4. 1-3 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	16 September 2015
In/Exclusion criteria	**Population**: Healthy adults **Intervention**: Include: drinking before diving. **Comparison**: not drinking **Outcome**: Include: decompression illness due to diving. Exclude: decompression illness due to high altitudes. **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available.

	An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Gempp, 2009, France	Experimental: randomized controlled trial (within subjects design)	8 healthy military divers, mean age 36±6 years. All subjects were trained divers and none experienced decompression sickness in the past. The dive protocol consisted of an open sea field dive to 30 msw breathing air for 30 min (sea temperature 14°C) with a decompression rate of 15 msw/min and a 9 min stop at 3 msw.	1. drinking 1300 ml of a water containing a saline-glucose formulation (157 meq/l Na^+ and 23 g/l carbohydrate (osmolality = 234 mOsm/l) 90 minutes before a dive (drinking time was 50-60 min)) 2. no prehydration The divers were not allowed to drink liberally after the dive session.	Mean bubble grade is expressed as KISS factor (Kissman Integrated Severity Score). This score takes into account the kinetics of the bubbles at different recording times and is assumed to be a meaningful linearized measure of post-decompression intravascular bubble activity status.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
mean bubble score	drinking 90 min before dive vs not drinking before dive	Statistically significant: 3.5 vs 19.4 MD: -15.9 £† (p=0.031) *In favour of drinking before diving*	1, 8 vs 8 § (within subjects design)	Gempp, 2009

£ No SD's and CI available

† Imprecision (lack of data)

§ Imprecision (limited sample size)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Gempp, 2009	Unclear, not mentioned	No, divers were not informed about which experimental conditions they were to dive under that day	No	No	within subjects design

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/lack of data
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is limited evidence in favour of drinking before diving. It was shown that drinking 1300 ml of a saline-glucose solution resulted in a statistically significant decrease of bubble production, compared to not drinking before diving (Gempp, 2009). Evidence is of low quality and results cannot be considered precise due to limited sample size and lack of data.
Reference(s)	**Individual studies** Gempp E, Blatteau JE, Pontier J-M, Louge P. *Preventive effect of pre-dive hydration on bubble formation in divers*. Br J Sports Med 2009, 43:224-228

Decompression illness – Exercise (Prevention)

Question (PICO)	In humans (P), is exercise before, during or after diving (I) compared to not doing this (C) effective to prevent a decompression accident (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Decompression sickness"] OR decompression:ti,ab,kw OR "caisson disease":ti,ab,kw OR [mh "embolism, air"] OR embolism:ti,ab,kw 2. [mh Diving] OR diving:ti,ab,kw 3. [mh Exercise] OR exercise:ti,ab,kw OR [mh Drinking] OR drink*:ti,ab,kw 4. 1-3 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Decompression sickness"[Mesh] OR decompression[TIAB] OR "caisson disease"[TIAB] OR "embolism, air"[Mesh] OR embolism[TIAB] 2. Diving[Mesh] OR diving[TIAB] 3. Exercise[Mesh] OR exercise[TIAB] OR Drinking[Mesh] OR drink*[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'decompression sickness'/exp OR decompression:ab,ti OR 'caisson disease':ab,ti OR 'air embolism'/exp OR embolism:ab,ti 2. diving/exp OR diving:ab,ti 3. exercise/exp OR exercise:ab,ti OR drinking/exp OR drinking:ab,ti 4. 1-3 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	16 September 2015
In/Exclusion criteria	**Population**: Healthy adults **Intervention**: Include: exercise before or during diving. **Comparison**: no exercise

	Outcome: Include: decompression illness due to diving. Exclude: decompression illness due to high altitudes. **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Blatteau, 2005, France	Experimental: Randomized controlled trial (within subjects design)	16 trained military divers, mean age 33.4 years, mean BMI 24 kg/m^2, who were medically fit for diving. None of them experienced decompression sickness (DCS) in the past. Subjects were asked to avoid physical exertion during the 2d that preceded the dive. Each diver performed two dives 3 days apart, one with and one without exercise 2 h before the dive.	1. Exercise before dive: single bout of submaximal exercise consisting of endurance running at an intensity of 60-80% if maximum theoretical heart rate (220-age) for a total exercise session of 45 min. 2. No exercise. Divers were compressed in a hyperbaric chamber to 30 msw, at a rate of 15 m/min, breathing air and remaining at pressure for 30 min. They were decompressed at a rate of 10 m/min to 3 msw, where they remained for 9 minutes before they were decompressed to the surface at the same rate.	Mean bubble grade is an indicator of venous gas bubble formation. The Spencer scale was used to evaluate the signals of bubbles and the determination of the bubble grade was carried out at 30 and 60 min after surfacing.
Blatteau, 2007, France	Experimental: Randomized controlled trial (within subjects design)	16 trained military divers, mean age 33.6±3.7 years, BMI 21-27.1 kg/m^2. None of them experienced DCS in the past. Subjects were asked to avoid physical exertion during the 2d that preceded the dive. Each diver performed two dives 3 days apart, one with and one	1. Exercise before dive: 40 min constant-load exercise, which consisted of an outdoor running beginning 2 h before the dive. After the exercise, divers were allowed to drink water liberally. 2. No exercise. Divers were compressed in a hyperbaric chamber to 400	KISS: Kisman Integrated Severity Score: assumed to be a meaningful linearized measurement of post-decompression intravascular bubble activity status.

		without exercise 2 h before the dive.	kPa, at a rate of 150 kPa/min, breathing air and remaining at pressure for 30 min. During bottom time, the participants exercised on a bicycle ergometer under aerobic threshold keeping their HR between 110-120 beats/min. They were decompressed at a rate of 100 kPa/min, with a 9 minute stop at 130 kPa.	
Castagna, 2011, France	Experimental: Randomized controlled trial (within subjects design)	24 healthy and physically active males with diving experience. Mean age 32.4±8.1 years, mean BMI 21.6±1.6 kg/m^2, mean % body fat 18.1±4.23. None of them had experienced DCS in the past. Each diver performed two dives (one with exercise and one without exercise before the dive) separated by a minimum of 48 h.	1. Exercise before dive: running on a treadmill for 45 min at a speed corresponding to their own VeT value, starting 1h before immersion. Subjects were allowed to drink mineral still water freely during the 15 min between the end of the exercise and the immersion. 2. No exercise before dive Dive was performed in open sea.	The ventilator threshold (VeT) of the participants was determined in a separate preliminary session. Quantity of bubbles was graded using the Spencer scale before being converted into KISS.
Dujić, 2004, Croatia	Experimental: Randomized controlled trial (within subjects design)	13 experienced divers, mean age 29.9±5 years, BMI 21.5-29.0 kg/m^2. None of them had experienced DCS in the past. Each diver performed two dives 7 days apart, one with and one without physical exercise 24 h before the dive.	1. Exercise before dive: treadmill running at 90% of maximum heart rate for 3 min followed by exercise at 50% of maximum heart rate for 2 min. This was repeated 8 times for a total exercise session of 40 min. 2. No exercise before dive. Divers were compressed in a hyperbaric chamber to 280 kPa at a rate of 100 kPa/min, breathing air and remaining at pressure for 80 min. They were then decompressed at a rate of 90 kPa/min to 130 kPa where they remained for 7 min before they were decompressed to the surface pressure (100 kPa) at the same rate.	Gas bubbles were seen as high intensity echoes in the right heart and the pulmonary artery. Monitoring was performed every 20 min for 80 min after reaching surface pressure.
Dujić, 2005, Croatia	Experimental: Randomized controlled trial	10 male military divers, mean age 35.1±4.3 year, BMI 22.5-29 kg/m^2, medically fit to dive based on the	1. Exercise during diving: fin swimming for 3 minutes during decompression stop	After the dive, subjects were placed in the left supine position and an

		annual medical examination and without any clinical signs of cardiopulmonary disease. Each diver performed two dives 3-7 days apart, one with and one without physical exercise during the 3 min decompression stop.	2. No exercise during diving: rest for 3 minutes during decompression stop Subjects dived to 400 kPa at a rate of 100 kPa/min breathing air, remaining at pressure for 30 min. The ascent up to the decompression stop at 130 kPa was 90 kPa/min where they remained for 3 min before they were decompressed to the surface pressure (100 kPa).	echocardiographic investigation with a phase array probe was performed. Monitoring was performed every 20 min for 60 min after reaching surface pressure.
Gennser, 2012, Sweden	Experimental: Randomized controlled trial	10 healthy male volunteers, mean age 40.6±9.5 years, mean BMI 27.71±3.7 kg/m^2 and mean % body fat 20.81±4.8. Five subjects had wet dive experience, while all except three had dry chamber experience. Each subject performed three dives with at least one week between dives. Subjects were asked to avoid all physical and sporting activities for at least 48 h prior to the dives or between exercise bouts.	1. Exercise 2 h before dive: 40 min submaximal work on a cycle ergometer. 2. Exercise 24 h before dive: 40 min submaximal work on a cycle ergometer 3. No exercise before dive Subjects were compressed with air in a hyperbaric chamber to 18 m (0.28 MPa) for 100 min and then decompressed at a rate of 15 m/min with stops at 6 m for 5 min and at 3 m for 15 min.	Exercise levels were set to the subject's maximum heart rate that was derived from the V_{O2max} which determined at least 1 week prior to the first dive. VGE (venous gas emboli) were evaluated using precordial Doppler ultrasound and measured on the Kisman Masurel scale. Measurements were made on resting subjects immediately (within 2 minutes) on surfacing, then at 5 min intervals until 30 min postdive, and at 15 min intervals thereafter for at least 2.5 h total until it could be safely said that the peak of VGE had been reached.

Jankowski, 1997, Canada	Experimental: Randomized controlled trial	29 healthy adult males (10 professional divers and 19 commercial diving students). A minimum of 36 h was required between the start of two consecutive experimental dives for any subject. Military divers generally had 2 days between dives, the commercial diving students had 1 week between consecutive dives. Participants were instructed to avoid strenuous physical activity, weight training and alcohol for 24 h before each experimental dive.	1. Arm exercise (n=5): custom-built paddle ergometer or lifting light weights 2. Leg exercise (n=11): submersible, electromagnetically braked bicycle ergometers 3. No exercise: 16 standby divers performed 28 control dives by remaining inactive Participants voluntarily performed a total of 44 air dives at a maximal pressure equivalent to 45 msw for 30 min, followed by a 55-min staged decompression. Beginning at minutes 7, 15, 25, 35 and 45 of the 55-min decompression period, randomly selected subjects performed intermittent 5-min periods of moderate arm or leg exercise.	Before beginning, physical work capacity of each subject for both arm and leg exercise was measured during 2 separate standardized, progressive, physical work-capacity test protocols. The amount of venous gas emboli (VGE) in each subject was determined within 30 min of ending the experimental dive and at 30-min intervals thereafter for the next 90 min using Doppler ultrasonic bubble detectors.
Jurd, 2011, UK	Experimental: Randomized controlled trial	15 male volunteers of the Royal Navy divers and QinetiQ staff with mixed wet- and dry-diving experience, mean age 36.5±8.5 years, mean BMI 26.3±1.6 kg/m^2, mean % body fat 18.8±3.0. Each subject conducted three dives and there were at least seven days between the dives. Each dive commenced at the same time each day to avoid any influence of circadian effects.	1. Exercise 2 h before dive 2. Exercise 24 h before dive 3. No exercise before dive Exercise regimen: jogging on the spot for 1 minute followed by 10 star jumps, repeated for a total of 40 min. They were asked to aim at 70% of their theoretical maximum heart rate (220-age beats/min) for the exercise period. Chamber dives were to 18 msw with a bottom time of 100 min. Decompression stops were at 6 msw for 5 minutes and 3 msw for 15 minutes, with an ascent rate of 15 msw/min.	VGE were scored using the Kisman-Masurel (KM) code and the KISS score was then calculated to give a linearized measure of VGE. Post-dive monitoring began within 2 min of surfacing and was carried out every 5 min for the first 30 min and very 15 min thereafter up to 180 min.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Mean bubble grade (spencer scale)	Exercise 2 h before dive vs no exercise before dive	Statistically significant: 0.44 vs 1.25 MD: -0.81 £† (p=0.0062) *In favour of exercise before dive*	1, 16 vs 16 § (within subjects design)	Blatteau, 2005
Mean bubble grade (KISS)		Statistically significant: 5.36 vs 12.26 MD: -6.9 £† (p<0.05) *In favour of exercise before dive*	1, 16 vs 16 § (within subjects design)	Blatteau, 2007
	Exercise 1h before dive vs no exercise before dive	Statistically significant: 14.7±12.3 vs 25.5±12.3 MD: -10.8 ££† (p<0.001) *In favour of exercise before dive*	1, 24 vs 24 § (within subjects design)	Castagna, 2011
Average number of bubbles/cm^2	Exercise 24h before dive vs no exercise before dive	Statistically significant: 0.22±0.26 vs 0.98±0.69 MD: -0.76 ££† (p<0.05) *In favour of exercise before dive*	1, 13 vs 13 § (within subjects design)	Dujić, 2004
Venous gas formation (median ± range)	Exercise during decompression stop vs no exercise during decompression stop	Statistically significant: 20 min after dive: 1.5±4 vs 2.5±4 MD: -1.0 (p=0.028) ££† *In favour of exercise during decompression stop* Statistically significant: 40 min after dive: 1±3 vs 2.5±4 MD: -1.5 (p=0.028) ££† *In favour of exercise during decompression stop* Not statistically significant: 60 min after dive: 1±3 vs 2±3 MD: -1.0 (p=0.076) ££†	1, 10 vs 10 § (within subjects design)	Dujić, 2005
KM score (median)	Exercise 2 h before dive vs exercise 24 h before dive vs no exercise	Not statistically significant: 3 vs 3 vs 2+ £ (p>0.05) †	1, 10 vs 10 vs 10 §	Gennser, 2012
KISS score (mean±SE)	Exercise (pooled) during decompression vs no exercise during decompression	Statistically significant: Precordial: 6.7±2.8 vs 14.4±3.1 MD: -7.7 ££† (p≤0.05) *In favour of exercise during decompression* Left subclavian: 1.6±1.0 vs 9.4±3.1 MD: -7.8 ££† (p≤0.05) *In favour of exercise during decompression*	1, 28 dives vs 16 dives § (performed by 29 subjects) (within subjects design)	Jankowski, 1997

		Right subclavian: 0.3±0.1 vs 14.2±3.2 MD: -13.9 ££† (p≤0.05) *In favour of exercise during decompression*		
mean KISS	Exercise 2 h before dive vs no exercise before dive	Statistically significant: 11.3 vs 17.2 MD: -5.9 £ (p<0.04) *In favour of exercise 2 h before dive*	1, 15 vs 15 § (within subjects design)	Jurd, 2011
	Exercise 24 h before dive vs no exercise before dive	Not statistically significant: 13.1 vs 17.2 MD: -4.1 £† (p>0.05)		

Mean ± SD unless otherwise stated
£ No SD's and CI available
†† No CI available
† Imprecision (lack of data)
§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Blatteau, 2005	Unclear, randomized, but mentioned how	Unclear, not mentioned	No	No	Within subjects design Simulated dive in hyperbaric chamber
Blatteau, 2007	Unclear, randomized, but mentioned how	Unclear, not mentioned	No	No	Within subjects design Simulated dive in hyperbaric chamber
Castagna, 2011	Unclear, not mentioned	Unclear, not mentioned	No	No	Within subjects design
Dujić, 2004	Unclear, randomized, but not mentioned how	Unclear, not mentioned	No	No	Within subjects design Simulated dive in hyperbaric chamber
Dujić, 2005	Unclear, randomized, but not mentioned how	Unclear, not mentioned	No	No	Within subjects design
Gennser, 2012	No, ab/ba crossover design	No, operators blinded to the order of the dives	No	No	within subjects design Simulated dive in hyperbaric chamber
Jankowski, 1997	Unclear, randomized but not mentioned how	Unclear, not mentioned	No	No	within subjects design Simulated dive in hyperbaric chamber

Jurd, 2011	Unclear, randomized but not mentioned how	No, operators were blinded to order of the divers	No	No	within subjects design Simulated dive in hyperbaric chamber

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/lack of data
Inconsistency	0	
Indirectness	-1	Dive was simulated in a hyperbaric chamber in most studies
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [C]**	

Conclusion	There is limited evidence in favour of exercise before diving or during decompression. In making this evidence conclusion, we place a higher value on studies that used running as exercise before diving over studies that used cycling as mode of exercise before diving, since running has more effect over cycling. It was shown that exercise before diving or during decompression resulted in a statistically significant decrease of venous gas emboli after decompression, compared to no exercise before or during diving (Blatteau 2005, Blatteau 2007, Castagna 2011, Dujić 2004, Dujić 2005, Jankowski 1997, Jurd 2011). A statistically significant decrease of venous gas emboli, using exercise 24 h prior to diving compared to no exercise, could not be demonstrated (Gennser 2012). However, in this study, they used cycling as mode of exercise instead of running, which seems to have an influence on VGE. Evidence is of very low quality and results cannot be considered precise due to limited sample size and lack of data.
Reference(s)	**Articles** Blatteau J-E, Gempp E, Galland F-M, Pontier J-M, Sainty J-M, Robinet C. *Aerobic exercise 2 hours before a dive to 30 msw decreases bubble formation after decompression*. Aviat Space Environ Med 2005, 76:666-9 Blatteau J-E, Boussuges A, Gempp E, Pontier J-M, Castagna O, Robinet C, Galland F-M, Bourdon L. *Haemodynamic changes induced by submaximal exercise before a dive and its consequences on bubble formation*. Br J Sports Med 2007, 41:375-379 Dujić Ž, Duplančic D, Marinovic-Terzić I, Baković D, Ivančev V, Valic Z, Eterović D, Petri NM, Wisløff U, Brubakk AO. *Aerobic exercise before diving reduces venous gas bubble formation in humans*. J Physiol 2004, 555.3: 637-642 Dujić Ž, Palada I, Obad A, Duplančic D, Baković D, Valic Z. *Exercise during a 3-min decompression stop reduces postdive venous gas bubbles*. Med Sci Sports Exerc 2005, 37(8): 1319-23 Gennser M, Jurd KM, Blogg SL. *Pre-dive exercise and post-dive evolution of venous gas emboli*. Aviat Space Environ Med 2012, 83:30-4 Jankowski LW, Nishi RY, Eaton DJ, Griffin AP. *Exercise during decompression reduces the amount of venous gas emboli*. Undersea Hyperbaric Med 1997, 24(2):59-65 Jurd KM, Thacker JC, Seddon FM, Gennser M, Loveman GAM. *The effect of pre-dive exercise timing, intensity and mode on post-decompression venous gas emboli*. Diving Hyperb Med 2011, 41(4):183-188

TRAVEL ILLNESSES

Altitude sickness – Descending (First Aid)

Question (PICO)	In humans with altitude sickness (P), is descending to a lower altitude (I) compared to not descending (C) effective for laypeople to change survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Altitude sickness"] OR ((altitude:ti,ab,kw OR mountain:ti,ab,kw) AND (sickness:ti,ab,kw OR disease:ti,ab,kw)) 2. [mh rest] OR rest:ti,ab,kw OR resting:ti,ab,kw OR descend*:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Altitude sickness"[Mesh] OR ((altitude[TIAB] OR mountain[TIAB]) AND (sickness[TIAB] OR disease[TIAB])) 2. Rest[Mesh] OR rest[TIAB] OR resting[TIAB] OR descend*[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'altitude disease'/exp OR (altitude NEXT/1 sickness):ab,ti OR (mountain NEXT/1 sickness):ab,ti OR (altitude NEXT/1 disease):ab,ti OR (mountain NEXT/1 disease):ab,ti 2. Rest/exp OR rest:ab,ti OR resting:ab,ti OR descend*:ab,ti 3. 1-2 AND
Search date	28 September 2015
In/Exclusion criteria	**Population**: People with altitude sickness **Intervention**: descending to a lower altitude. **Comparison**: not descending, staying at the same altitude. **Outcome**: acute mountain sickness, high-altitude headache. **Study design:** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Bärtsch, 1993, Germany	Experimental: randomized controlled trial	Subjects were recruited from mountaineers who spend a night in the Capanna "Regina Margherita" located at an altitude of 4559 m (barometric pressure 430-440 mm Hg) in the Alps Valais. 31 subjects were treated with maximum pressure (193 mbar), mean age 31 (range 19-52 yr), 25 males, 6 females; 23 subjects were treated at minimum pressure (20 mbar), mean age 30 (range 18-47 yr), 14 males, 9 females; 10 subjects rested at the ambient pressure in the supine position, mean age 33 (range 18-54 yr), 10 males.	1. 193 mbar = descend of 2250 m 2. 20 mbar = descend of 250 m 3. Rest = ambient pressure	clinical score for AMS was measured as well as the AMS-C score immediately after treatment and 12 hours after treatment

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Clinical score	193 mbar vs 20 mbar vs rest	Immediately after treatment: Statistically significant: 1.4, 95%CI [1.1; 1.6] vs 2.7, 95%CI [2.1; 3.3] vs 2.7, 95%CI [0.95; 1.77] (p<0.001) £† *In favour of 193 mbar* 12 hours after treatment: Not statistically significant: 2.5, 95%CI [1.8; 3.2] vs 3.1, 95%CI [2.4; 3.9] vs 2.3, 95%CI [2.1; 3.3] (p=0.29) £†	1, 31 vs 23 vs 10 §	Bärtsch, 1993
AMS-C	193 mbar vs 20 mbar vs rest	Immediately after treatment: Statistically significant: 0.81, 95%CI [0.56; 1.07] vs 1.13, 95%CI [0.77; 1.48] vs 1.20, 95%CI [0.95; 1.77] (p<0.005) £† *In favour of 193 mbar and 20 mbar* 12 hours after treatment: Not statistically significant: 1.02, 95%CI [0.87; 1.31] vs 1.36, 95%CI [0.87; 1.86] vs 0.92, 95%CI [0.43; 1.41] (p=0.09) £†		

£ No SD's available

† Imprecision (lack of data)

§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Bärtsch, 1993	No, randomization in blocks, treatment assigned by drawing from envelope	No, subjects were unaware of what pressure had been applied	No	No	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/lack of data
Inconsistency	0	
Indirectness	-1	descend was simulated in hyperbaric chamber
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is limited evidence in favour of descending 2250 m. It was shown that 193 mbar (equivalent to a descend of 2250 m) resulted in a statistically significant decrease immediately after treatment of clinical score for mountain sickness and AMS-C, compared to rest at ambient pressure (= not descending) (Bärtsch, 1993). A statistically significant decrease of clinical score and AMS-C after twelve hours, using 193 or 20 mbar compared to rest at ambient pressure (= not descending), could not be demonstrated (Bärtsch, 1993). Evidence is of low quality and results cannot be considered precise due to limited sample size and lack of data.
Reference(s)	**Articles** Bärtsch P, Merki B, Hofstetter D, Maggiorini M, Kayser B, Oelz O. *Treatment of acute mountain sickness by simulated descent: a randomized controlled trial*. BMJ 1993, 306:1098-101

Altitude sickness – Resting (First Aid)

Question (PICO)	In humans with altitude sickness (P), is resting (I) compared to not resting (C) effective for laypeople to change survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Altitude sickness"] OR ((altitude:ti,ab,kw OR mountain:ti,ab,kw) AND (sickness:ti,ab,kw OR disease:ti,ab,kw)) 2. [mh rest] OR rest:ti,ab,kw OR resting:ti,ab,kw OR descend*:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Altitude sickness"[Mesh] OR ((altitude[TIAB] OR mountain[TIAB]) AND (sickness[TIAB] OR disease[TIAB])) 2. Rest[Mesh] OR rest[TIAB] OR resting[TIAB] OR descend*[TIAB] 3. 1-2 AND

	Embase (via Embase.com interface) using the following search strategy: 1. 'altitude disease'/exp OR (altitude NEXT/1 sickness):ab,ti OR (mountain NEXT/1 sickness):ab,ti OR (altitude NEXT/1 disease):ab,ti OR (mountain NEXT/1 disease):ab,ti 2. Rest/exp OR rest:ab,ti OR resting:ab,ti OR descend*:ab,ti 3. 1-2 AND
Search date	28 September 2015
In/Exclusion criteria	**Population**: healthy people **Intervention**: resting **Comparison**: not resting **Outcome**: acute mountain sickness, high-altitude headache. **Study design:** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Altitude sickness – Descending (Prevention)

Question (PICO)	In humans with mild symptoms of altitude sickness (P), is descending (I) compared to not descending (C) effective to prevent acute mountain sickness (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Altitude sickness"] OR ((altitude:ti,ab,kw OR mountain:ti,ab,kw) AND (sickness:ti,ab,kw OR disease:ti,ab,kw)) 2. [mh rest] OR rest:ti,ab,kw OR resting:ti,ab,kw OR descend*:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Altitude sickness"[Mesh] OR ((altitude[TIAB] OR mountain[TIAB]) AND (sickness[TIAB] OR disease[TIAB])) 2. Rest[Mesh] OR rest[TIAB] OR resting[TIAB] OR descend*[TIAB]

	3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'altitude disease'/exp OR (altitude NEXT/1 sickness):ab,ti OR (mountain NEXT/1 sickness):ab,ti OR (altitude NEXT/1 disease):ab,ti OR (mountain NEXT/1 disease):ab,ti 2. Rest/exp OR rest:ab,ti OR resting:ab,ti OR descend*:ab,ti 3. 1-2 AND
Search date	28 September 2015
In/Exclusion criteria	**Population**: People with altitude sickness **Intervention**: descending to a lower altitude. **Comparison**: not descending, staying at the same altitude. **Outcome**: acute mountain sickness, high-altitude headache. **Study design:** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Altitude sickness – Interventions to prevent hypothermia/heatstroke (Prevention)

Question (PICO)	In humans with altitude sickness (P), which interventions (I) are effective to prevent hypothermia or heatstroke (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Altitude sickness"] OR ((altitude:ti,ab,kw OR mountain:ti,ab,kw) AND (sickness:ti,ab,kw OR disease:ti,ab,kw)) 2. [mh hypothermia] OR hypothermia:ti,ab,kw OR [mh heatstroke] OR heatstroke:ti,ab,kw OR hyperthermia:ti,ab,kw OR "heat stroke":ti,ab,kw 3. 1-2 AND

	MEDLINE (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Altitude sickness"[Mesh] OR ((altitude[TIAB] OR mountain[TIAB]) AND (sickness[TIAB] OR disease[TIAB])) 2. hypothermia[Mesh] OR hypothermia[TIAB] OR heatstroke[Mesh] OR heatstroke[TIAB] OR hyperthermia[TIAB] OR "heat stroke"[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'altitude disease'/exp OR (altitude NEXT/1 sickness):ab,ti OR (mountain NEXT/1 sickness):ab,ti OR (altitude NEXT/1 disease):ab,ti OR (mountain NEXT/1 disease):ab,ti 2. hypothermia/exp OR hypothermia:ab,ti OR 'heat stroke'/exp OR heatstroke:ab,ti OR (heat NEXT/1 stroke):ab,ti OR hyperthermia:ab,ti 3. 1-2 AND
Search date	25 September 2015
In/Exclusion criteria	**Population**: people with altitude sickness **Intervention**: interventions to prevent hypothermia or hyperthermia/heatstroke **Comparison**: doing nothing **Outcome**: hypothermia or hyperthermia/heatstroke **Study design:** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Altitude sickness – Ascending slowly (Prevention)

Question (PICO)	In humans (P), is ascending slowly (I) compared to ascending fast (C) effective to prevent altitude sickness (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy:

	1. [mh "Altitude sickness"] OR ((altitude:ti,ab,kw OR mountain:ti,ab,kw) AND (sickness:ti,ab,kw OR disease:ti,ab,kw)) 2. ascen*:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Altitude sickness"[Mesh] OR ((altitude[TIAB] OR mountain[TIAB]) AND (sickness[TIAB] OR disease[TIAB])) 2. ascen*[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'altitude disease'/exp OR (altitude NEXT/1 sickness):ab,ti OR (mountain NEXT/1 sickness):ab,ti OR (altitude NEXT/1 disease):ab,ti OR (mountain NEXT/1 disease):ab,ti 2. ascen*:ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	14 October 2015
In/Exclusion criteria	**Population**: Include: Healthy people with previous and regular mountaineering experience. Exclude: Subjects with cardiac or respiratory disease or regular intake of any medication, subjects with a history of high altitude pulmonary oedema, severe acute mountain sickness at altitudes below 3500 m, or high altitude cerebral oedema. **Intervention**: slow ascent **Comparison**: fast ascent **Outcome**: acute mountain sickness (AMS) **Study design:** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Bloch, 2009, Switzerland	Experimental: Randomized controlled trial	34 healthy volunteers, 27 men and 7 women, aged 45±11 yr (range 25-65 yr). Baseline characteristics were collected in Switzerland, the study took place on	1. Fast ascent (n=18): ascended to camp I (5533 m) once for 2 nights before the final ascent from base camp toward the summit was undertaken, with 2 nights at 5533 m, 2 nights at camp II (6265 m) and 1 night at camp II (6865 m) reaching the summit of Muztagh Ata (7546 m) on day 15.	Due to bad weather conditions at camp II (6265 m), the fast group was forced to return to base camp (4497 m) at

		the Mustagh Ata in China.	2. Slow ascent (n=16): same protocol except this group ascended twice to camp I for 2 nights. Further ascent was the same, reaching the summit on day 19. After a flight from Zurich (490 m) to Islamabad Pakistan (500 m), a 1-week bus trip to Subash (3730 m), China, was undertaken. The participants slept at altitudes between 500 and 3730 m, and mean ascent rate was 463 m/24 h during this period for both groups.	day 14 for 3 nights.
Hsu, 2015, Taiwan	Experimental: randomized controlled trial	91 young adults were recruited from college mountaineering clubs in Taiwan. Participants were divided into 2 groups by choice: group 1 = fast ascent (3 days; n=43), group 2 = slow ascent (4 days, n=48)	1. Fast ascent: climbed to a mountain shelter at 3350 m within 2nd day. During the 3rd day, they hiked 4.6 km at an altitude between 3200 m en 3400 m to the lakeside at 3310 m. On the fourth day, they returned to the mountain shelter after hiking 4.6 km. On the fifth day, they returned to the trail head. 2. Slow ascent: climbed to 2850 m within 2nd day. During the 3rd day, they continued climbing to the mountain shelter at 3350 m. On the fourth day, they hiked a total of 13.32 km from the mountain shelter to the lakeside and back to the shelter at 2850 m. On the fifth day, they returned to the trail head. Both groups started from the trailhead after an overnight stay (2370 m).	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
AMS-C score at summit (7546 m)	Slow ascent vs fast ascent	Statistically significant: 0.303±0.105 vs 0.453±0.128 MD: -0.15, 95%CI [-0.23;0.07] (p=0.0002)* *In favour of slow ascent*	1, 16 vs 18 §	Bloch, 2009
Success (= reaching at least camp III (6865 m))		Statistically significant: 15/16 vs 11/18 OR: 9.55, 95%CI [1.02;89.22] (p=0.0479) *In favour of slow ascent*		
AMS positive		Not statistically significant: 9/48 vs 10/43 0.76, 95%CI [0.28;2.10]* (p=0.616) ¥	1, 48 vs 43 §	Hsu, 2015

Mean ± SD (unless otherwise indicated)
* Calculations done by the reviewer(s) using Review Manager software
¥ Imprecision (large variability of results)
§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Bloch, 2009	Yes, allocation based on the choice of participants	Yes, participants chose for themselves in which group they would participate	No, loss of participants was clearly described	No	The fast ascent group did not complete the protocol, but multiple regression analysis showed this had no influence on the outcome.
Hsu, 2015	Yes, allocation based on the choice of participants	Yes, participants chose for themselves in which group they would participate	No	No	Not controlled for medication taken during ascent. Hydration status was not taken into account.

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/large variability of the results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is limited evidence in favour of a slow ascent. It was shown that a slow ascent resulted in a statistically significant decrease of acute mountain sickness, compared to a fast ascent (Bloch 2009). Furthermore, it was shown that a slow ascent resulted in a statistically significant increase of success, compared to a fast ascent (Bloch 2009). However, in a second study, not controlling for important confounders, a statistically significant decrease of AMS positive individuals, using a slow ascent compared to a fast ascent, could not be demonstrated (Hsu 2015). Evidence is of low quality and results cannot be considered precise due to limited sample size and/or large variability of results.
Reference(s)	**Articles** Bloch KE, Turk AJ, Maggiorini M, Hess T, Merz T, Bosch MM, Barthelmes D, Hefti U, Pichler J, Senn O, Schoch OD. *Effect of ascent protocol on acute mountain sickness and success at Muztagh Ata, 7546 m*. High Altitude Medicine & Biology 2009, 10(1):25-32 Hsu T-Y, Weng Y-M, Chiu Y-H, Li W-C, Chen P-Y, Wang S-H, Huang K-F, Kao W-F, Chiu T-F, Chen J-C. *Rate of ascent and acute mountain sickness at high altitude*. Clin J Sport Med 2015, 25(2):95-104

Altitude sickness – Drinking (Prevention)

Question (PICO)	In humans (P), is drinking adequate amounts (I) compared to not drinking (C) effective for the prevention of altitude sickness (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Altitude sickness"] OR ((altitude:ti,ab,kw OR mountain:ti,ab,kw) AND (sickness:ti,ab,kw OR disease:ti,ab,kw)) 2. [mh drinking] OR drink*:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Altitude sickness"[Mesh] OR ((altitude[TIAB] OR mountain[TIAB]) AND (sickness[TIAB] OR disease[TIAB])) 2. drinking[Mesh] OR drink*[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'altitude disease'/exp OR (altitude NEXT/1 sickness):ab,ti OR (mountain NEXT/1 sickness):ab,ti OR (altitude NEXT/1 disease):ab,ti OR (mountain NEXT/1 disease):ab,ti 2. drinking/exp OR drink*:ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	13 October 2015
In/Exclusion criteria	**Population**: Healthy people. **Intervention**: drinking adequate amounts (at least 3 L) **Comparison**: not drinking or drinking less than 3 L **Outcome**: acute mountain sickness (AMS) **Study design:** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Nerín, 2006, Spain	Observational: cohort study	9 healthy, male Caucasian mountaineers (age range 28-44 years) were studied on a 7 day mountaineering expedition in the	≤3000 mL mean fluid intake vs >3000 mL mean fluid intake	Symptoms or signs of AMS according to the Lake

		Pamir during which they climbed to altitudes above 7000 m. Each day of each mountaineer was included in the study as a "case" but only those for whom data were available for all the variables in the model (36 cases), including symptoms or signs of AMS.		Louise consensus score: AMS was defined as moderate if the score was 4 to 6 and severe if the score was ≥7

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Mean acute mountain sickness symptoms	≤3000 mL mean fluid intake vs >3000 mL mean fluid intake	Not statistically significant: 1.375 vs 0.91666 £ MD: 0.45834 ££ (p=0.0882) †	1, 24 vs 12 §	Nerín, 2006

£ No SD available
†† No CI available
† Imprecision (lack of data)
§ Imprecision (limited sample size)

Quality of evidence

Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations
Nerín, 2006	Unclear	No	Unclear	No	

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Limited sample size, lack of data
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Conclusion	There is limited evidence neither for the benefit or harm of drinking adequate amounts of fluids nor for not drinking adequate amounts of fluids. A statistically significant decreased risk of acute mountain sickness in case of drinking adequate amounts of fluids compared to not drinking adequate amounts could not be demonstrated (Nerín 2006). Evidence is of very low quality and results of this study are imprecise due to limited sample size and lack of data.
Reference(s)	**Individual studies** Nerín MA, Palop J, Montaño JA, Morandeira JR, Vaázquez M. *Acute Mountain Sickness: Influence of Fluid Intake*. Wilderness and Environmental Medicine 2006, 17:215-220

Altitude sickness – Alcohol (Risk Factor)

Question (PICO)	In humans (P), is drinking alcohol (I) a risk factor for altitude sickness (O) compared to not drinking alcohol (C)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Altitude sickness"] OR ((altitude:ti,ab,kw OR mountain:ti,ab,kw) AND (sickness:ti,ab,kw OR disease:ti,ab,kw)) 2. [mh "alcohol drinking"] OR alcohol:ti,ab,kw OR (sleep*:ti,ab,kw AND (pill*:ti,ab,kw OR medication:ti,ab,kw)) 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Altitude sickness"[Mesh] OR ((altitude[TIAB] OR mountain[TIAB]) AND (sickness[TIAB] OR disease[TIAB])) 2. "alcohol drinking"[Mesh] OR alcohol[TIAB] OR (sleep*[TIAB] AND (pill*[TIAB] OR medication[TIAB])) 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'altitude disease'/exp OR (altitude NEXT/1 sickness):ab,ti OR (mountain NEXT/1 sickness):ab,ti OR (altitude NEXT/1 disease):ab,ti OR (mountain NEXT/1 disease):ab,ti 2. 'drinking behavior'/exp OR alcohol:ab,ti OR (sleep* NEXT/1 pill*):ab,ti OR (sleep* NEXT/1 medication):ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in MEDLINE (via PubMed interface).
Search date	25 September 2015
In/Exclusion criteria	**Population**: healthy people **Risk factor**: Alcohol intake **Outcome**: acute mountain sickness **Study design:** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Risk factor	Remarks
Schneider, 2002, Germany	Experimental: cohort study	2 studies were performed: study 1 (n=440; 73 females, 359 males; mean age 37.0±11.4 yr) in the summer of 1996 and 1998; study 2 (n=387; 81 females, 314 males; mean age 38.2±11.5 yr) in the summer of 2000. All were mountaineers who had ascended to the Capanna Margherita (at 4559 m) in Italy to stay overnight. AMS was assessed the next morning.	≤150 g alcohol/wk vs >150 g alcohol/wk	AMS = acute mountain sickness. 150 g alcohol per week amounts to a daily intake of 0.2 L of wine or 0.5 L of beer.

Synthesis of findings

Outcome	Risk factor	Effect Size	#studies, # participants	Reference
AMS (%)	≤150 g/wk vs >150 g/wk	Study 1: Not statistically significant: 26±5 vs 36±12 MD: -10.0 (p>0.05) £†λ Study 2: Not statistically significant: 30±5 vs 33±13 MD: -3.0 (p>0.05) £†λ	1, 440 (no information on how many participants in each group) 1, 387 § (no information on how many participants in each group)	Schneider, 2002

Mean ± SD (unless otherwise indicated)
£ No CI's available
† Imprecision (lack of data)
§ Imprecision (limited sample size or low number of events)
λ Data extracted from graph

Quality of evidence

Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations
Schneider, 2002	No	No	Yes, data from univariate analysis	No	

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/low number of events/lack of data
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Conclusion	There is limited evidence neither for the benefit or harm of drinking >150g alcohol/week nor drinking ≤150 g alcohol/week. A statistically significant increased risk of acute mountain sickness in case of drinking >150g alcohol/week compared to drinking ≤150 g alcohol/week could not be demonstrated (Schneider 2002).

	Evidence is of very low quality and results of this study are imprecise due to limited sample size and lack of data.
Reference(s)	**Articles** Schneider M, Bernasch D, Weymann J, Holle R, Bärtsch P. *Acute mountain sickness: influence of susceptibility, preexposure and ascent rate*. Med Sci Sports Exerc 2002, 34(12):1886-1891.

Altitude sickness – Sleeping medication (Risk Factor)

Question (PICO)	In humans (P), is the use of sleeping medication (I) a risk factor for altitude sickness (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Altitude sickness"] OR ((altitude:ti,ab,kw OR mountain:ti,ab,kw) AND (sickness:ti,ab,kw OR disease:ti,ab,kw)) 2. [mh "alcohol drinking"] OR alcohol:ti,ab,kw OR (sleep*:ti,ab,kw AND (pill*:ti,ab,kw OR medication:ti,ab,kw)) 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Altitude sickness"[Mesh] OR ((altitude[TIAB] OR mountain[TIAB]) AND (sickness[TIAB] OR disease[TIAB])) 2. "alcohol drinking"[Mesh] OR alcohol[TIAB] OR (sleep*[TIAB] AND (pill*[TIAB] OR medication[TIAB])) 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'altitude disease'/exp OR (altitude NEXT/1 sickness):ab,ti OR (mountain NEXT/1 sickness):ab,ti OR (altitude NEXT/1 disease):ab,ti OR (mountain NEXT/1 disease):ab,ti 2. 'drinking behavior'/exp OR alcohol:ab,ti OR (sleep* NEXT/1 pill*):ab,ti OR (sleep* NEXT/1 medication):ab,ti 3. 1-2 AND
Search date	25 September 2015
In/Exclusion criteria	**Population**: Healthy people **Risk factor**: Sleeping medication **Comparison**: no sleeping medication **Outcome**: acute mountain sickness, high-altitude headaches **Study design:** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Motion sickness – Travel activities (First Aid)

Question (PICO)	In humans with motion sickness (P), are certain travel activities (I) compared to other travel activities (C) more effective to reduce symptoms of motion sickness (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Motion sickness"] OR ((motion:ti,ab,kw OR sea:ti,ab,kw OR air:ti,ab,kw OR train:ti,ab,kw OR car:ti,ab,kw OR travel:ti,ab,kw) AND sickness:ti,ab,kw) OR kinetosis:ti,ab,kw 2. distraction*:ti,ab,kw OR read*:ti,ab,kw OR breath*:ti,ab,kw OR music:ti,ab,kw OR activit*:ti,ab,kw OR behavior*:ti,ab,kw OR respiration:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Motion sickness"[Mesh] OR ((motion[TIAB] OR sea[TIAB] OR air[TIAB] OR train[TIAB] OR car[TIAB] OR travel[TIAB]) AND sickness[TIAB]) OR kinetosis[TIAB] 2. distraction*[TIAB] OR read*[TIAB] OR breath*[TIAB] OR music[TIAB] OR activit*[TIAB] OR behavior*[TIAB] OR respiration[TIAB] **3.** 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'motion sickness'/exp OR ((motion:ab,ti OR sea:ab,ti OR air:ab,ti OR train:ab,ti OR car:ab,ti OR travel:ab,ti) AND sickness:ab,ti) OR kinetosis:ab,ti 2. distraction*:ab,ti OR read*:ab,ti OR breath*:ab,ti OR music:ab,ti OR activit*:ab,ti OR behavior*:ab,ti OR respiration:ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	26 October 2015
In/Exclusion criteria	**Population**: Include: Healthy people. **Intervention**: Include: Travel activities such as reading, listening to music, controlled breathing, counting. **Comparison**: Include: spontaneous breathing, no intervention. **Outcome**: Include: Symptoms of motion sickness, nausea **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched.

	An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Denise, 2009, UK	Experimental: randomized controlled trial (within subjects design)	16 subjects (7 males, 9 females, age range 21-59, mean age 29 years) with high motion sickness susceptibility. Motion was produced by a SEGA360 flight simulator. Subjects were seated, tilted 30° backward from machine/seat upright (0° reference position) and exposed to sinusoidal pitch oscillations at ±30° peak displacement. A simultaneous sinusoidal roll oscillation was added to the motion to enhance the provocation.	1. Spontaneous breathing 2. In phase synchronization: subjects were cued to begin inspiration by a brief tone presented each time they were momentarily 60° down backwards (= in-phase because it is the usual spontaneous pattern of entrainment of breathing with passive tilting motion) 3. Out of phase synchronization: subject began inspiration when momentarily upright, before the onset of backwards tilt. 4. Desynchronization: the pacing of respiratory frequency with a beep was slightly increased for half of the subject (and decreased for the other half) such that an 18° phase drift occurred for each tilt cycle.	
Jokerst, 1999, USA	Experimental: randomized controlled trial	46 healthy undergraduate students (17 male, ages 17-26), who were susceptible to motion sickness. Participants sat stationary on a stool within a rotating optokinetic drum with alternating vertical black and white stripes lining	1. Slow deep breathing (n=18): inhale for approximately 4 s and exhale for 4 s. 2. Counting breaths (n=16): subjects were asked to count their breaths and asked for the count every 3 min.	

		the interior of the drum. Drum rotation speed was 10 rotations/minute.	3. Control (n=12): subjects breathed normally.	
Yen Pik Sang, 2003a, UK	Experimental: randomized controlled trial (within subjects design)	24 volunteers, 10 males and 14 females, mean age 27±7 years, range 20-55 years. Motion sickness was provoked by whole body rotation coupled with head movements that generated cross-coupled stimulation of the labyrinth.	1. Controlled breathing: focus and control breathing, try to breathe gently and regularly 2. Listening to music: commercially available audiotape 3. Control: no intervention	
Yen Pik Sang, 2003b, UK	Experimental: randomized controlled trial (within subjects design)	12 healthy volunteers, 8 women and 4 men, 19-54 yr old (mean 30.8±9.52 years). Subjects were seated, restrained, in a SEGA ™360 flight simulator and exposed to angular pitch oscillation at ±20° peak displacement, 25°/s peak velocity, 0.2 Hz, for a maximum of 30 min.	1. Counting: subjects counted backwards tilts of the simulator once mild nausea developed. 2. Control: subjects underwent motion alone.	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Time to moderate nausea (min)	Spontaneous breathing vs in phase vs out of phase vs desynchronization	Statistically significant: 15.75±9.60 vs 18.38±10.52 vs 19.94±9.83 vs 22.00±9.68 (p<0.001) £ *In favour of controlled breathing (out of phase & desynchronization)*	1, 16 vs 16 § (within subjects design)	Denise, 2009
	controlled breathing vs control	Statistically significant: 10.7±5.6 vs 9.2±5.9 MD: 1.7 (p<0.01) ££ *In favour of controlled breathing*	1, 24 vs 24 § (within subjects design)	Yen Pik Sang, 2003a
	listening to music vs control	Statistically significant: 10.4±5.6 vs 9.2±5.9 MD: 1.2 (p<0.01) ££ *In favour of listening to music*		
Mean Subjective symptoms of motion sickness (SSMS) score	Slow deep breathing vs control	Statistically significant: 5.35±2.9 vs 7.83±3.3 MD: -2.48, 95%CI [-4.78; -0.18] (p=0.03)* *In favour of slow deep breathing*	1, 18 vs 12 §	Jokerst, 1999
	Counting breaths vs control	Not statistically significant: 9.06±5.8 vs 7.83±3.3 MD: 1.23, 95%CI [-2.17; 4.63] (p=0.48)* ¥	1, 16 vs 12 §	
Total motion sickness symptom score	Counting vs control	Not statistically significant: 24.5±7.0 vs 24.33±5.1 MD: 0.17 (p>0.05) ££†	1, 12 vs 12 § (within subjects design)	Yen Pik Sang, 2003b

Mean ± SD (unless otherwise indicated)

* Calculations done by the reviewer(s) using Review Manager software
£ No effect size or CI available
££ No CI available
¥ Imprecision (large variability of results)
† Imprecision (lack of data)
§ Imprecision (limited sample size)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Denise, 2009	No, Williams square design	Unclear, not mentioned	No	No	within subjects design
Jokerst, 1999	Unclear, randomized but not mentioned how	Unclear, not mentioned	No	No	
Yen Pik Sang, 2003a	No, order was balanced	Yes, not possible	No	No	within subjects design
Yen Pik Sang, 2003b	No, order was counterbalanced	Yes, but not possible	unc		

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/lack of data/large variability of the results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	**Controlled breathing**: There is limited evidence in favour of controlled breathing. It was shown that controlled breathing resulted in a statistically significant increase of time to moderate nausea and a decrease of mean subjective symptoms of motion sickness, compared to control (Denise 2009, Jokerst 1999, Yen Pik Sang 2003a). Evidence is of low quality and results cannot be considered precise due to limited sample size. **Activities**: There is limited evidence in favour of listening to music. It was shown that listening to music resulted in a statistically significant increase of time to moderate nausea (Yen Pik Sang 2003a). However, a statistically significant decrease of motion sickness symptoms, using counting compared to not counting, could not be demonstrated (Jokerst 1999, Yen Pik Sang 2003b). Evidence is of low quality and results cannot be considered precise due to limited sample size, lack of data and/or large variability of results.
Reference(s)	**Articles** Denise P, Vouriot A, Normand H, Golding JF, Gresty MA. *Effect of temporal relationship between respiration and body motion on motion sickness*. Auton Neurosci 2009, 151:142-146

	Jokerst MD, Gatto M, Fazio R, Stern RM, Kock KL. *Slow deep breathing prevents the development of tachygastria and symptoms of motion sickness*. Aviat Space Environ Med 1999, 70(12):1189-92 Yen Pik Sang FD, Billar JP, Golding JF, Gresty MA. *Behavioral Methods of Alleviating Motion Sickness: Effectiveness of Controlled Breathing and a Music Audiotape*. J Travel Med 2003a, 10:108-111 Yen Pik Sang FD, Golding JF, Gresty MA. *Suppression of Sickness by Controlled Breathing During Mildly Nauseogenic Motion*. Aviat Space Environ Med 2003b, 74(9):998-1002

Travel illness – Seating position (Prevention)

Question (PICO)	In humans (P), is a certain seating position or view (I) compared to another seating position or view (C) effective to prevent motion sickness (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Motion sickness"] OR ((motion:ti,ab,kw OR sea:ti,ab,kw OR air:ti,ab,kw OR train:ti,ab,kw OR car:ti,ab,kw OR travel:ti,ab,kw) AND sickness:ti,ab,kw) OR kinetosis:ti,ab,kw 2. seat*:ti,ab,kw OR view*:ti,ab,kw OR visual:ti,ab,kw OR vision:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Motion sickness"[Mesh] OR ((motion[TIAB] OR sea[TIAB] OR air[TIAB] OR train[TIAB] OR car[TIAB] OR travel[TIAB]) AND sickness[TIAB]) OR kinetosis[TIAB] 2. seat*[TIAB] OR view*[TIAB] OR visual[TIAB] OR vision[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'motion sickness'/exp OR ((motion:ab,ti OR sea:ab,ti OR air:ab,ti OR train:ab,ti OR car:ab,ti OR travel:ab,ti) AND sickness:ab,ti) OR kinetosis:ab,ti 2. seat/exp OR seat*:ab,ti OR visual:ab,ti OR vision:ab,ti OR view*:ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	21 October 2015
In/Exclusion criteria	**Population**: Include: Healthy people. **Intervention**: Include: Certain seating positions, fixated view point, outside view. **Comparison**: Include: other seating positions, no fixated view points, inside view. **Outcome**: Include: Symptoms of motion sickness, nausea, mean illness rating, misery scale, wellbeing scale. **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available.

	Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Bos, 2005, The Netherlands	Experimental: Randomized controlled trial (within subjects design)	24 subjects (14 women, 10 male; 28.3±9.3 yr (range 21-57 yr)) were seated in a ship motion simulator (SMS) back-to-back approximately 6 m apart at the far left and right sides, symmetrically with respect to the bridge. They were sitting on a stable chair with back and arm rests, but no head or shoulder support. All simulated pitch, roll and yaw motions were within ±15°, surge and sway motions within ±2 m, and heave motion within ±0.5 m. One 30-min interval was arbitrarily chosen and used for all conditions.	1. "OUT": out-the-window view of a true Earth-fixed visual environment 2. "IN": bridge was adequately illuminated and the outside view completely darkened. No outside structures were visible. 3. "BLIND": subjects were blindfolded All subjects participated in all conditions at approximately the same time of day with no more than 1 d in between two conditions.	Subjective misery scale (MISC) was recorded
Butler, 2006, UK	Experimental: non-randomized controlled trial	120 male subjects between 18 and 26 yr of age from the student population of the University of Southampton, were seated in a cabin on a rigid seat with a flat horizontal supporting surface 445 mm above the floor. Subjects were exposed to sinusoidal fore-and-aft oscillation at 0.1 Hz with an acceleration magnitude of 0.89 m/s rms (a displacement of ±3.18 m) for 30 min.	1. Internal view of simple shapes (triangle, circle, cross, square) 2. External view of simple shapes 3. External view of 6 horizontal black lines 4. External view of the laboratory 5. Blindfolded 6. Collimated view of simple shapes n=20 in each group.	Studies have suggested that motion sickness may be influenced by fore-and aft acceleration at frequencies up to about 0.1 Hz.
Butler, 2009, UK	Experimental: non-randomized controlled trial	120 male subjects between 18 and 26 yr of age from the student population of the University of Southampton, were seated in a cabin on a rigid seat with a flat horizontal supporting surface 445 mm above the floor. Subjects were exposed to sinusoidal fore-and-aft oscillation at 0.1 Hz with an	1. Internal view of simple shapes + in-phase pitch 2. Blindfolded + in-phase pitch 3. External view of the laboratory+ in-phase pitch	

		acceleration magnitude of 0.89 m/s rms (a displacement of ±3.18 m) combined with ±3.69° pitch displacement. For 3 groups, the pitch displacement was 180°C out of phase with the fore-and-aft oscillation so that the resultant peak acceleration was 1.89 m/s. 3 other groups experienced the same fore-and-aft and pitch oscillations, but with the two motions presented out of phase, so that the resultant peak acceleration was 0.63 m/s). Subjects were exposed to the movements for 30 min.	4. Internal view of simple shapes + out-of-phase pitch 5. Blindfolded + out-of-phase pitch 6. External view of the laboratory + out-of-phase pitch [only data on view were extracted]	
Griffin, 2004, UK	Experimental: Non-randomized controlled trial	300 subjects in 15 independent groups of 20 subjects each participated in the study. All subjects were male, aged 18-26 yr (except for experiment 4, where 10 men and 10 women in each condition participated). The study was undertaken using two types of vehicle from one manufacturer: a car and a MPV (multipurpose vehicle = minivan). Subjects sat alone in the rear seats. The vehicles were driven on roads around suburban Southampton at variable speeds up to 30 mph. The fixed route involved corners and junctions, with occasional short delays for traffic, but no roundabouts. The journey lasted 30 minutes.	Experiment 1: 1. Normal viewing condition 2. Blindfolded 3. No outside view 4. No forward view 5. Narrow forward view Passengers were seated in central rear seat of the car. Experiment 2: 1. Car: rear central seat 2. Car: directly behind driver 3. Car: behind driver and contact with head rest 4. Car: stationary (rear central seat) 5. MPV: first row of seats (directly behind driver) 6. MPV: second row of seats (behind driver)	
Mills, 2000, UK	Experimental: Non-randomized controlled trial	72 male subjects (aged 18-25 years) were randomly selected from the student population of the University of Southampton. Oscillations were generated using a simulator capable of horizontal vibration with displacements up to 1 m. Subjects sat on a chair within a rigid cabin supported on the vibrator table. Fore-and-aft or lateral motion was achieved by rotating the chair through 90°.	1. Fore-and-aft: high backrest with harness, eyes open 2. Fore-and-aft: low backrest with lap belt, eyes open 3. Fore-and-aft: low backrest with lap belt, eyes closed 4. Lateral: high backrest with harness, eyes open	

		Subjects were assigned to 6 groups of 12 subjects.	5. Lateral: low backrest with lap belt, eyes open 6. Lateral: low backrest with lap belt, eyes closed	
Rolnick, 1989, Israel	Experimental: Randomized controlled trial (within subjects design)	12 paid volunteers (20-26 years old, 6 males, 6 females) were seated in a tilting room which tilts around an axis at floor level. A He/Ne laser beam was projected onto a rapidly rotating mirror which produced a continuous line image around the four walls of the tilting room. The laser was mounted alternately on a fixed horizontal frame, resulting in a stable artificial horizon during room tilt, or on the floor of the tilting room, resulting in a room-fixed projection.	1. No motion: the subject was seated in the tilting room without motion of the room. 2. Closed cabin: The subject was seated in the tilting room, the artificial horizon device was fixated to the floor and motion took place. 3. Artificial horizon: the subject was seated in the room, the artificial horizon device was fixated to a stationary horizontal platform 4. Windows: the subject was seated looking at the doors and both doors were open allowing a good view into the main laboratory room.	
Rolnick, 1991, Israel	Experimental: Randomized controlled trial	44 males, aged 19-25 years with sailing experience were randomly divided in two groups and were seated on two chairs mounted on the device (a rotatable platform with an earth-vertical axis of rotation) in such a way that the centre of each chair was situated 50 cm off the axis of rotation. Subjects wore a head-yoking device, designed to ensure that both subjects performed the same head movement. Subjects were rotated for 6 min, during which they were asked to perform head movements every 15 s.	1. Controlling subject: Use over joystick, which controlled the direction of rotation, its velocity, and the rate of deceleration for stops. 2. Non-controlling subject: exposed to the same stimulus, but was not able to control rotation or head movements.	Head-yoking device: two helmets connected from top centre to top centre by a 71 cm metal rod.
Stern, 1990, UK	Experimental: Randomized controlled trial	45 students, 23 male and 22 female, were seated on a stool with his/her chin resting on a chinrest within a circular vection	3. Control: unobstructed visual field of the inner surface of the optokinetic drum	

		drum. The drum rotation speed was 60°/s.	4. Restricted field: subjects wore goggles which effectively provided a circular field stop which limited the visual field to 15° 5. Fixation group: subjects fixated on a 1 cm black cross located 25 cm in front of their eyes and 10 cm from the surface of the drum.	
Wada, 2012, Japan	Experimental: Randomized controlled trial (within-subjects design)	10 healthy individuals, 9 males and 1 female, 21.5±1.0 years, were exposed to an acceleration stimulus as passengers seated in the automobile navigator seat. The experimental course was a quasi-oval track with straight parts approximately 100 m in length and curved parts of 8 m and 10 m radii. Located in each straight segment were five pylons with 15-m gaps. The driver drove the track continuously at approximately 30 km/h through the pylon slalom in the straight segment and at approximately 15 km/h in the curved segments. The track distance was 260 m. Each driving trial was terminated after 20 laps.	1. Active condition: tilt head against the centrifugal acceleration, thus imitating the driver's head tilt 2. Natural condition: sit naturally, relax, not oppose the lateral acceleration intentionally	
Webb, 2002, UK	Experimental: Non-randomized controlled trial (within-subjects design)	18 subjects were seated on a chair in a optokinetic drum. Exposure duration was 30 min.	1. Optokinetic stimulus: black and white stripes moving 2. Stationary fixation point: same stimulus but with a superimposed stationary cross.	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
View:				
MISC (Misery Scale)	OUT vs IN	after 2-5 min: Statistically significant: MISC worse in IN ¤ ($p<0.0008$) £ *In favour of OUT* after 15-30 min:	1, 24 vs 24 § (within subjects design)	Bos, 2005

		Statistically significant: MISC worse in IN ¤ (p<0.03) £ *In favour of OUT*		
	OUT vs BLIND	after 2-5 min: Statistically significant: MISC worse in BLIND ¤ (p<0.002) £ *In favour of OUT* after 15-30 min: Statistically significant: MISC worse in OUT ¤ (p<0.02) £ *In favour of BLIND*		
Mean illness rating	1. Internal view of simple shapes 2. External view of simple shapes 3. External view of 6 horizontal black lines 4. External view of the laboratory 5. Blindfolded 6. Collimated view of simple shapes	Not statistically significant: No difference between the groups ¤ (p=0.957) £†	1, 120 (20 subjects in each group) §	Butler, 2006
	External vs internal view	Statistically significant: (p=0.001) ¤ *In favour of external view*	1, 20 vs 20 §	Butler, 2009
	External view vs blindfold	Not statistically significant: (p=0.308) ¤ £†		
	Normal view vs narrow forward view	Not statistically significant: 0.40 vs 0.54 λ† (p>0.3) ¤	1, 20 vs 20 §	Griffin, 2004 Experiment 1
	Normal or narrow view vs blindfold, no outside view or no forward view	Statistically significant: 0.40 or 0.54 vs 1.22 or 1.03 λ† (p<0.02) ¤ *In favour of normal or narrow view*		
	eyes open vs eyes closed (low backrest)	fore-and-aft motion: Not statistically significant: 2.09±1.64 vs 1.63±1.51 MD: 0.46, 95%CI [-0.80; 1.72] (p=0.47) *¥	1, 12 vs 12 §	Mills, 2000
		lateral motion Not statistically significant: 1.46±1.11 vs 1.20±0.92 MD: 0.26, 95%CI [-0.56; 1.08] (p=0.53) *¥	1, 12 vs 12 §	
Mean accumulated illness rating	fixation point vs no fixation point	Statistically significant: 19.4 vs 40.7 MD: -21.3 ££ (p<0.01) *In favour of fixation point*	1, 18 vs 18 § (within subjects design)	Webb, 2002
Relative motion sickness score (after 30 min exposure)	Artificial horizon vs closed cabin	Statistically significant: 1.79 vs 4.0 MD: -2.21 (p<0.05) λ££ *In favour of artificial horizon*	1, 12 vs 12 § (within subjects design)	Rolnick, 1989
	Windows vs closed cabin	Statistically significant:		

		1.93 vs 4.0 MD: -2.07 (p<0.05) λ££ *In favour of windows*		
	Artificial horizon vs windows	Not statistically significant: 1.79 vs 1.93 MD: -0.14 (p>0.05) λ££†		
Mean subjective symptoms of motion sickness (after 12 min rotation)	Restricted/fixation vs control	Statistically significant: 0.9±0.3 vs 7.8±0.9 MD: -6.9, 95%CI [-7.38; -6.42] (p<0.00001)* *In favour of restricted/fixation*	1, 15 vs 15 §	Stern, 1990
Nausea	Restricted/fixation vs control	Statistically significant: 0/15 vs 8/15 OR: 0.03 (p<0.05) *In favour of restricted/fixation*		
Seating:				
Mean illness rating	car: rear central seat vs directly behind driver vs directly behind driver + headrest	Not statistically significant: 0.8 vs 0.96 vs 1.22 λ† (p>0.05) ¤	1, 20 vs 20 §	Griffin, 2004 Experiment 2
	MPV: first row vs second row	Not statistically significant: 0.7 vs 0.68 λ† (p>0.05) ¤		
	high backrest vs low backrest (eyes open)	fore-and-aft motion: Statistically significant: 0.74±1.0 vs 2.09±1.64 MD: -1.35, 95%CI [-2.44; -0.26] (p=0.01) * *In favour of high backrest*	1, 12 vs 12 §	Mills, 2000
		lateral motion Not statistically significant: 1.02±0.94 vs 1.46±1.11 MD: -0.44, 95%CI [-1.26; 0.38] (p=0.29) *¥	1, 12 vs 12 §	
Self-driving:				
Motion sickness symptoms	Controllability vs no-controllability	Statistically significant: 1.7 vs 2.3 MD: 0.7 ££ (p<0.05) *In favour of controllability*	1, 22 vs 22 §	Rolnick, 1991
Mean wellbeing score (0 = good, 8 = bad)		Statistically significant: 5.19±0.81 vs 7.57±1.08 MD: -2.38 £££ (p<0.001) *In favour of controllability*		
Total symptom score	Active vs natural condition	5 min after driving termination: Statistically significant: 1.78±1.97 vs 3.94±2.91 MD: -2.16 λ£££ (p=0.011) *In favour of active condition* 10 min after driving termination:	1, 10 vs 10 § (within subjects design)	Wada, 2012

		Statistically significant: 1.13±0.89 vs 2.34±1.88 MD: -1.21 λ£££ (p=0.034) *In favour of active condition*		

Mean ± SD (unless otherwise indicated)
* Calculations done by the reviewer(s) using Review Manager software
£ No raw data/SD's/effect size/CI available
££ No SD's and CI available
£££ No CI available
¥ Imprecision (large variability of results)
† Imprecision (lack of data)
§ Imprecision (limited sample size or low number of events)
¤ Data graphically represented in article.
λ Data extracted from graph

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
View:					
Bos, 2005	No, conditions were randomized	Yes, but not possible	No	No	within subjects design, simulated motion of a boat and no true external view
Butler, 2006	Yes, first 7 subjects allocated to condition 1, next 7 to condition 2,…	Yes, but not possible	No	No	simulated car motion and no true external view
Butler, 2009	Yes, first 7 subjects allocated to condition 1, next 7 to condition 2,…	Yes, but not possible	No	No	simulated motion and no true external view
Griffin, 2004	Unclear, not mentioned	Yes, but not possible	No	No	
Mills, 2000	Unclear, not mentioned	Yes, but not possible	No	No	Simulation of motion
Stern, 1990	Unclear, randomized, but not mentioned how	Yes, but not possible	No	No	Simulation of motion and view
Rolnick, 1989	No, conditions were counterbalanced	yes but irrelevant, all subjects was tested in all conditions	No	No	Simulation of motion within subjects design
Webb, 2002	Unclear, not mentioned	Yes, but not possible	No	No	Simulation of motion and view within subjects design
Seating:					
Griffin, 2004	Unclear, not mentioned	Yes, but not possible	No	No	
Mills, 2000	Unclear, not mentioned	Yes, but not possible	No	No	Simulation of motion
Self-driving:					

Rolnick, 1991	Unclear, randomized but not mentioned how	Yes, participants knew if they were in control or not	No	No	
Wada, 2012	Unclear, not mentioned	Yes, participants knew which intervention was tested	No	No	within subjects design

Level of evidence
View:

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/lack of data/large variability of the results
Inconsistency	0	
Indirectness	-1	simulation of motion and no true external view
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Seating:

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/lack of data/large variability of the results
Inconsistency	0	
Indirectness	-1	Simulation of motion in one study
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Self-driving

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	**<u>View:</u>** There is limited evidence in favour of outside viewing, restricted visual field and fixation to a central point. It was shown that outside viewing resulted in a statistically significant decrease of misery, compared to inside viewing (Bos 2005, Butler 2009, Rolnick 1989). It was shown that restriction of the visual field or fixation on a central point resulted in a statistically significant decrease of mean illness rating, subjective symptoms of motion sickness or nausea compared to normal, unobstructed visual field, no fixation point or no outside view (Griffin 2004, Stern 1990, Webb 2002). It was shown that looking at the horizon resulted in a statistically significant decrease of motion sickness, compared to no outside view (Rolnick 1989). However, a statistically significant decrease of motion sickness, looking at the horizon compared to outside view, could not be demonstrated (Rolnick 1989).

	Furthermore, a statistically significant decrease of mean illness rating, using external view compared to internal view, could not be demonstrated (Butler 2006). Also, a statistically significant decrease of mean illness rating, using internal or external view compared to blindfold; using normal view compared to narrow forward view or having the eyes open compared to having the eyes closed, could not be demonstrated (Griffin 2004, Mills 2000). Evidence is of very low quality and results cannot be considered precise due to limited sample size and/or lack of data. **Seating**: There is limited evidence in favour of high backrest. It was shown that a high backrest resulted in a statistically significant decrease of mean illness rating, compared to a low backrest (Mills 2000). There is limited evidence neither in favour of sitting in the central rear seat nor sitting behind the driver. A statistically significant decrease of mean illness rating, sitting in the rear central seat of a car compared to sitting directly behind the driver, could not be demonstrated (Griffin 2004). Furthermore, a statistically significant decrease of mean illness rating, sitting on the first row of a MPV compared to sitting on the second row of a MPV could not be demonstrated (Griffin 2004). Evidence is of very low quality and results of these studies are imprecise due to limited sample size, lack of data and/or large variability of results. **Self-driving**: There is limited evidence in favour of self-driving. It was shown that having control over the movements resulted in a statistically significant decrease of motion sickness symptoms and mean well-being score, compared to no control. Furthermore, it was shown that moving as the driver resulted in a statistically significant decrease in total symptom score, compared to moving as the passenger (passive movement following the centrifugal acceleration) (Rolnick 1991, Wada 2012). Evidence is of low quality and results cannot be considered precise due to limited sample size.
Reference(s)	**Articles** Bos JE, MacKinnon SN, Patterson A. *Motion Sickness Symptoms in a Ship Motion Simulator: Effects of Inside, Outside, and No View*. Aviat Space Environ Med 2005, 76(12):1111-8 Butler CA, Griffin MJ. *Motion Sickness During Fore-and-Aft Oscillation: Effect of the Visual Scene*. Aviat Space Environ Med 2006, 77(12):1236-43 Butler CA, Griffin MJ. *Motion Sickness with Combined Fore-Aft and Pitch Oscillation: Effect of Phase and the Visual Scene*. Aviat Space Environ Med 2009, 80(11):946-54 Griffin MJ, Newman MM. *Visual Field Effects on Motion Sickness in Cars.* Aviat Space Environ Med 2004, 75(9):739-48 Mills KL, Griffin MJ. *Effect of Seating, Vision and Direction of Horizontal Oscillation on Motion Sickness*. Aviat Space Environ Med 2000, 71(10):996-1002 Rolnick A, Bles W. *Performance and Well-Being Under Tilting Conditions: The Effects of Visual Reference and Artificial Horizon*. Aviat Space Environ Med 1989, 60:779-85 Rolnick A, Lubow RE. *Why is the driver rarely motion sick? The rol of controllability in motion sickness.* Ergonomics 1991, 34(7):867-879 Stern RM, Hu S, Anderson RB, Leibowitz HW, Koch KL. *The Effects of Fixation and Restricted Visual Field on Vection-Induced Motion Sickness*. Aviat Space Environ Med 1990, 61:712-5 Wada T, Konno H, Fujisawa S, Doi S. *Can Passengers' Active Head Tilt Decrease the Severity of Carsickness? Effect of Head Tilt on Severity of Motion Sickness in a Lateral Acceleration Environment.* Hum factors 2012, 54(2):226-234 Webb NA, Griffin MJ. *Optokinetic Stimuli: Motion Sickness, Visual Acuity, and Eye Movements*. Aviat Space Environ Med 2002, 73(4):351-8

Motion sickness – Eating or drinking (Prevention)

Question (PICO)	In humans (P), is eating or drinking before travelling (I) compared to not eating or drinking (C) effective to prevent motion sickness (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Motion sickness"] OR ((motion:ti,ab,kw OR sea:ti,ab,kw OR air:ti,ab,kw OR train:ti,ab,kw OR car:ti,ab,kw OR travel:ti,ab,kw) AND sickness:ti,ab,kw) OR kinetosis:ti,ab,kw 2. [mh "Food and beverages"] OR [mh eating] OR food:ti,ab,kw OR eat*:ti,ab,kw OR [mh drinking] OR drink*:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Motion sickness"[Mesh] OR ((motion[TIAB] OR sea[TIAB] OR air[TIAB] OR train[TIAB] OR car[TIAB] OR travel[TIAB]) AND sickness[TIAB]) OR kinetosis[TIAB] 2. "Food and beverages"[Mesh] OR eating[Mesh] OR food[TIAB] OR eat*[TIAB] OR drinking[Mesh] OR drink*[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'motion sickness'/exp OR ((motion:ab,ti OR sea:ab,ti OR air:ab,ti OR train:ab,ti OR car:ab,ti OR travel:ab,ti) AND sickness:ab,ti) OR kinetosis:ab,ti 2. food/exp OR eating/exp OR drinking/exp OR food:ab,ti OR eat*:ab,ti OR drink*:ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	16 October 2015
In/Exclusion criteria	**Population** Include: Healthy people **Intervention**: Include: eating or drinking before travelling **Comparison**: Include: Not eating or drinking before travelling **Outcome**: Include: motion sickness. Exclude: space sickness, post-operative nausea, nausea caused by radio- or chemotherapy. **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Feinle, 1995, UK	Experimental: Randomized controlled trial (within subjects design)	12 healthy male volunteers, aged 22-36 years. Subjects were seated vertically with their head and shoulders positioned inside a vection drum. The inner surface was painted with alternating black and white vertical stripes. The drum was rotated by an electric motor for 30 minutes at a constant rate (10 rpm).	1. Zero Fat liquid Meal (ZFM): 1.5 g carbohydrate, 3.6 g protein, 21 kcal, diluted with 150 g water 2. High Fat liguid Meal (HFM): 1.5 g carbohydrate, 3.6 g protein, 30 g margarine, 241 kcal, diluted with 120 g water The experiment was performed immediately after ingestion (protocol 1) or after a delay (protocol 2; for ZFM: 25 min, HFM: 90 min)	Studies took place at least 1 week apart and in a randomized order.
Levine, 2004, USA	Experimental: randomized controlled trial (within subjects design)	18 healthy undergraduate college students (15 females, 3 males), mean age 18.4 years (range 18-20 yr). A rotating optokinetic drum was used. Participants sat with their heads positioned in the centre of the cylinder, which was painted in alternating black and white stripes. The drum was rotated at a constant speed of 60°/s (10 rpm). 5 min after completion of the meal, participants were seated in the motionless drum for a 6-min baseline period. Participants were then exposed to the rotating drum for 16 min.	1. Protein-predominant meal (53% protein, 12% carbohydrate, 3.5% fat): 4.5 tablespoons of Designer chocolate whey protein powder, 5 teaspoons of heavy whipping cream, 4 teaspoons of Hershey chocolate syrup, 288 mL of water. 2. Carbohydrate meal (100% carbohydrate): 0.5 teaspoons of Hi-C concentrated lemonade powder, 7 tablespoons of granulated sugar, 300 mL of water. 3. No meal	
Lien, 2003, Taiwan	Experimental: randomized controlled trial (within subjects design)	18 healthy volunteers with a history of motion sickness (8 men, 10 women; aged 18-40 years). At 30 min postprandial, subjects were seated in the centre of a drum, the interior of which was painted with alternating black and white vertical stripes. The drum was	1. 1000 mg ginger capsules 2. 2000 mg ginger capsules 3. Placebo: identical looking capsules After an overnight fast, subjects ingested a 1000 kcal mixed solid-liquid meal: bacon and cheese sandwich on buttered	Before enrolment, subjects underwent circular vection to determine individual motion sickness susceptibility. Of the 18

		rotated clockwise at 60°/S for 15 min or until the subject reported severe nausea. After cessation of drum rotation, the subject remained in the drum for 15 min.	white bread, scrambled eggs, milkshake and water (25% protein, 30% carbohydrate, 45% fat).	subjects, 13 developed moderate to severe nausea within 15 min of vection induction. These 13 were included in the study to evaluate the effect of ginger.
Hu, 1998, China	Experimental: randomized controlled trial (within subjects design)	27 undergraduate students (11 men and 16 women; mean age 20.5±1.9 yr) Subjects sat on a chair in a circular vection drum. Alternation black and white vertical stripes covered the inner surface. The drum was rotated at a speed of 60°/s for 16 minutes each session.	1. 300 ml milk 2. 300 ml water 3. Nothing 15 minutes after drinking milk or water (or nothing) the subject viewed the optokinetic rotating drum for 16 min in each session. Symptoms of motion sickness were ascertained at 2-min intervals during the period of drum rotation. Only data at the end of drum rotation (16 min) were extracted.	The order of drinking milk, water or nothing was balanced with a Latin Square Design.
Uijtdehaage, 1992, USA	Experimental: randomized controlled trial	40 college students (21 males and 19 females; 19.3±1.7 years). Subjects were seated inside the circular vection drum. The interior was covered with alternating black and white vertical stripes. The drum was rotated clockwise at 10 rotations/min.	1. Breakfast (n=20): 18 g of cereal with 75 ml milk, a doughnut, and 200 ml of orange juice (= app. 60% carbohydrates, 30% fat, 10% protein). 2. No breakfast (n=20): read a newspaper for 10 min. Experimental procedure: baseline period (8 min) after which the meal group was fed, second 8 min postprandial period, 8 min "drum-off" period, 16 min "drum-on" period. Every 2 min the subjects reported their subjective symptoms of motion sickness.	
Williamson, 2005, USA	Experimental: randomized controlled trial	108 healthy college students (68 female and 40 male; age range 18-	1. Boost: 'low protein/ high carbohydrate' group: 12 g protein,	Power analysis, based on a

		23 years). N=27 in each group. Participants sat with their heads positioned in the center of the circular vection drum. The interior was covered with alternating black and white vertical stripes. The drum was rotated for 16 min at a constant speed of 60°/s (10 rpm).	49.2 g carbohydrate, 4.8 g fat 2. ProMod: 'high protein/low carbohydrate' group: 41.5 g protein, 22.5 g carbohydrate, 5.13 g fat 3. ProSure: 'moderate protein/moderate carbohydrate' group: 17 g protein, 44 g carbohydrate, 7 g fat 4. 300 ml Water Each 300 ml test drink contained 300 kcal. There was a 30 min interval between ingestion and rotation.	related study (Levine et al, 2004) indicated the appropriate number of subjects to use in this design to be 27 participants per group

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Nausea (100 mm VAS scale), median	zero fat liquid meal vs high fat liquid meal	Protocol 1: Not statistically significant: (median, interquartile range): 35.4 (11.8; 56.36) vs 28.2 (5.45; 45.45) λ££† (p>0.05) Protocol 2: Statistically significant: 18.33 (5.0; 33.33) vs 58.33 (42.55; 70.83) λ££ (p<0.05) *In favour of zero fat liquid meal*	1, 9 vs 9 § (within subjects design)	Feinle, 1995
Subjective symptoms of motion sickness (SSMS) scores (mean±SEM)	carbohydrate vs no meal	Not statistically significant: 9.0±0.8 vs 9.5±1.0 λ MD: -0.5 (p>0.05) ££†	1, 18 vs 18 § (within subjects design)	Levine, 2004
	Protein vs no meal	Statistically significant: 7.0±1.0 vs 9.5±1.0 λ MD: -2.5 (p<0.001) ££ *In favour of protein*		
	Protein vs carbohydrate	Statistically significant: 7.0±1.0 vs 9.0±0.8 λ MD: -2.0 (p=0.03) ££ *In favour of protein*		
Subjective symptoms of motion sickness	breakfast vs no breakfast	Statistically significant: 2.85±2.51 vs 4.55±2.78 MD: -1.70, 95%CI [-3.34; -0.06] (p=0.04)* *In favour of breakfast*	1, 20 vs 20 §	Uijtdehaage, 1992
Maximum subjective symptoms of motion sickness	ProMod vs water	Statistically significant: 4.4±2.08 vs 6.8±2.08 MD: -2.40, 95%CI [-3.51, -1.29] (p<0.0001)* λ *In favour of ProMod*	1, 27 vs 27 (power analysis)	Williamson, 2005
	ProSure vs water	Statistically significant:		

		3.6±2.08 vs 6.8±2.08 MD: -3.20, 95%CI [-4.31, -2.09] (p<0.00001)* λ *In favour of ProSure*		
	Boost vs water	Not statistically significant: 6.7±2.08 vs 6.8±2.08 MD: -0.10, 95%CI [-1.21, 1.01] (p=0.86)* λ		
Max nausea score during vection	1000 mg ginger vs placebo	Statistically significant: 1.7±0.3 vs 2.5±0.2 MD: -0.8 ££ (p<0.05) *In favour of 1000 mg ginger*	1, 13 vs 13 § (within subjects design)	Lien, 2003
	2000 mg ginger vs placebo	Statistically significant: 1.8±0.20 vs 2.5±0.2 MD: -0.7 ££ (p<0.05) *In favour of 2000 mg ginger*		
Latency to mild nausea (min)	1000 mg ginger vs placebo	Statistically significant: 8.5±1.1 vs 5.6±0.6 MD: 2.9 ££ (p<0.05) *In favour of 1000 mg ginger*		
	2000 mg ginger vs placebo	Statistically significant: 9.7±1.1 vs 5.6±0.6 MD: 4.1 ££ (p<0.05) *In favour of 2000 mg ginger*		
Nausea score after vection (VAS; mm)	1000 mg ginger vs placebo	Statistically significant: 0 min after vection 55.7±8.6 vs 85.7±2.9 MD: -30.0 ££ λ (p<0.05) *In favour of 1000 mg ginger* 15 min after vection 22.9±5.7 vs 38.6±10.0 MD: -15.7 ££ λ (p<0.05) *In favour of 1000 mg ginger* 30 min after vection 8.6±2.8 vs 25.7±5.7 MD: -17.1 ££ λ (p<0.05) *In favour of 1000 mg ginger* 45 min after vection 4.3±1.4 vs 11.4±2.9 MD: -7.1 ££ λ (p<0.05) *In favour of 1000 mg ginger*		
	2000 mg ginger vs placebo	Statistically significant: 0 min after vection 51.4±8.6 vs 85.7±2.9 MD: -34.3 ££ λ (p<0.05) *In favour of 1000 mg ginger*		

		15 min after vection 17.1±5.7 vs 38.6±10.0 MD: -21.5 ££ λ (p<0.05) *In favour of 1000 mg ginger* 30 min after vection 5.7±2.8 vs 25.7±5.7 MD: -20.0 ££ λ (p<0.05) *In favour of 1000 mg ginger* 45 min after vection 4.3±1.4 vs 11.4±2.9 MD: -7.1 ££ λ (p<0.05) *In favour of 1000 mg ginger* Not statistically significant: 60 min after vection No difference between ginger and placebo (p>0.05)		
Score of symptoms of motion sickness (mean±SE)	milk vs nothing	Not statistically significant: 4.5±0.8 vs 4.9±0.9 MD: -0.4 ££† (p>0.05) (scores at other time points are also not statistically significant)	1, 27 vs 27 § (within subjects design)	Hu, 1998
	water vs nothing	Not statistically significant: 4.6±0.9 vs 4.9±0.9 MD: -0.3 ££† (p>0.05) (scores at other time points are also not statistically significant)		
	milk vs water	Not statistically significant: 4.5±0.8 vs 4.6±0.9 MD: -0.1 ££† (p>0.05) (scores at other time points are also not statistically significant)		

Mean ± SD (unless otherwise indicated)
* Calculations done by the reviewer(s) using Review Manager software
£ No SD's available
££ No effect size and/or CI available
¥ Imprecision (large variability of results)
† Imprecision (lack of data)
§ Imprecision (limited sample size or low number of events)
λ Data extracted from graph

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Feinle, 1995	No, randomized order	No, unaware of effect of high fat on severity of nausea	No	Yes, 12 volunteers included in study, but only data from 9 participants mentioned	Within subjects design
Levine, 2004	No, order of conditions was counterbalanced	Unclear, not mentioned	No	No	Within subjects design
Lien, 2003	No, tests were performed in a randomized, double-blinded, crossover fashion	No, double-blinded	No	No	Within subjects design
Hu, 1998	No, Latin square	Yes, subjects could if they were drinking milk or water (or nothing)	No	No	Within subjects design
Uijtdehaage, 1992	Yes, based on habits of participants (normally eats breakfast or not)	Yes, not possible to blind having breakfast or not having breakfast	No	No	
Williamson, 2005	No, modified random assignment.	No, the test drinks looked identical. Research assistant did not know content of drinks.	No	No	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/lack of data/large variability of the results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is limited evidence in favour of **eating** before travelling. It was shown that a zero fat meal resulted in a statistically significant decrease of nausea, compared to a high fat meal (Feinle 1995). It was shown that a high protein meal resulted in a statistically significant decrease of subjective symptoms of motion sickness (SSMS), compared to no meal or a 100% carbohydrate meal (Levine 2004). It was shown that eating breakfast resulted in a statistically significant decrease of SSMS, compared to not eating breakfast (Uijtdehaage 1992). It was shown that a high protein/low carbohydrate meal or a low protein/high carbohydrate meal resulted in a statistically significant decrease of SSMS, compared to water (Williamson 2005).

	A statistically significant decrease of SSMS, using a 100% carbohydrate meal or a moderate protein/moderate carbohydrate meal compared to no meal or water, could not be demonstrated (Levine 2004, Williamson 2005). Evidence is of very low quality and results cannot be considered precise due to limited sample size, lack of data and/or large variability of results. There is limited evidence in favour of intake of **ginger** before travelling. It was shown that a 1000 or 2000 mg ginger intake resulted in a statistically significant decrease of nausea during and after vection, compared to placebo (Lien 2003). It was shown that a 1000 or 2000 mg ginger intake resulted in a statistically significant increase of latency to mild nausea, compared to placebo (Lien 2003). Evidence is of very low quality and results cannot be considered precise due to limited sample size, lack of data and/or large variability of results. There is limited evidence neither in favour of **drinking** water or milk nor drinking nothing. A statistically significant decrease of SSMS, drinking milk or water compared to drinking nothing, could not be demonstrated (Hu 1998). Evidence is of very low quality and results of this study are imprecise due to limited sample size and lack of data.
Reference(s)	**Articles** Feinle C, Grundy D, Read NW. *Fat increases vection-induced nausea independent of changes in gastric emptying*. Physiology & Behavior 1995, 58(6):1159-1165 Levine ME, Muth ER, Williamson MJ, Stern RM. *Protein-predominant meals inhibit the development of gastric tachyarrhythmia, nausea and the symptoms of motion sickness*. Aliment Pharmacol Ther 2004, 19:583-590 Lien H-C, Sun WM, Chen Y-H, Kim H, Hasler W, Owyang C. *Effects of ginger on motion sickness and gastric slow-wave dysrhythmias induced by circular vection*. Am J Physiol Gastrointest Liver Physiol 2003, 284:G481-G489 Hu S, Lagomarsino JJ, Luo Y-J. *Drinking milk or water has no effect on the severity of optokinetic rotation-induced symptoms of motion sickness.* Aviat Space Environ Med 1998, 69(12):1158-1161 Uijtdehaage SJ, Stern RM, Koch KL. *Effects of eating on vection-induced motion sickness, cardiac vagal tone, and gastric myoelectric activity.* Psychophysiology 1992, 29(2):193-201

Motion sickness – Location on boat (Prevention)

Question (PICO)	In humans (P), is a certain place on a boat (I) compared to another place on a boat (C) effective to prevent motion sickness (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Motion sickness"] OR ((motion:ti,ab,kw OR sea:ti,ab,kw OR air:ti,ab,kw OR train:ti,ab,kw OR car:ti,ab,kw OR travel:ti,ab,kw) AND sickness:ti,ab,kw) OR kinetosis:ti,ab,kw 2. seat*:ti,ab,kw OR view*:ti,ab,kw OR visual:ti,ab,kw OR vision:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy:

	1. "Motion sickness"[Mesh] OR ((motion[TIAB] OR sea[TIAB] OR air[TIAB] OR train[TIAB] OR car[TIAB] OR travel[TIAB]) AND sickness[TIAB]) OR kinetosis[TIAB] 2. seat*[TIAB] OR view*[TIAB] OR visual[TIAB] OR vision[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'motion sickness'/exp OR ((motion:ab,ti OR sea:ab,ti OR air:ab,ti OR train:ab,ti OR car:ab,ti OR travel:ab,ti) AND sickness:ab,ti) OR kinetosis:ab,ti 2. seat/exp OR seat*:ab,ti OR visual:ab,ti OR vision:ab,ti OR view*:ab,ti 3. 1-2 AND
Search date	21 October 2015
In/Exclusion criteria	**Population**: Include: Healthy people. **Intervention**: Include: Certain positions on a boat. **Comparison**: Include: other positions on a boat. **Outcome**: Include: Symptoms of motion sickness, nausea, mean illness rating, misery scale, wellbeing scale. **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Motion sickness – Wristband (Prevention)

Question (PICO)	In humans (P), are wristbands (I) compared to no wristbands (C) effective to prevent motion sickness (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Motion sickness"] OR ((motion:ti,ab,kw OR sea:ti,ab,kw OR air:ti,ab,kw OR train:ti,ab,kw OR car:ti,ab,kw OR travel:ti,ab,kw) AND sickness:ti,ab,kw) OR kinetosis:ti,ab,kw

	2. [mh Acupressure] OR acupressure:ti,ab,kw OR acustimulation:ti,ab,kw OR wristband*:ti,ab,kw or wrist band*:ti,ab,kw or bracelet*:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Motion sickness"[Mesh] OR ((motion[TIAB] OR sea[TIAB] OR air[TIAB] OR train[TIAB] OR car[TIAB] OR travel[TIAB]) AND sickness[TIAB]) OR kinetosis[TIAB] 2. acupressure[Mesh] OR acupressure[TIAB] OR acustimulation[TIAB] OR wristband*[TIAB] OR wrist band*[TIAB] OR bracelet*[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'motion sickness'/exp OR ((motion:ab,ti OR sea:ab,ti OR air:ab,ti OR train:ab,ti OR car:ab,ti OR travel:ab,ti) AND sickness:ab,ti) OR kinetosis:ab,ti 2. acupressure/exp OR acupressure:ab,ti OR acustimulation:ab,ti OR wristband*:ab,ti OR (wrist NEXT/1 band*):ti,ab OR bracelet*:ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	21 October 2015
In/Exclusion criteria	**Population**: Include: Healthy people. **Intervention**: Include: acupressure with a wristband. Exclude: electrical acustimulation. **Comparison**: Include: no acupressure. **Outcome**: Include: motion sickness, nausea. Exclude: postoperative nausea, nausea caused by radio- or chemotherapy, nausea not caused by motion. **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Alkaissi, 2005, Sweden	Experimental: Randomized controlled trial	60 female students and staff at the University Hospital, mean age 29±6 years, with a history of motion sickness. 10 women with high susceptibility and 10 women with low susceptibility to motion	1. P6 acupressure: SeaBand® with a plastic pearl that applies pressure on P6. 2. Non-acupressure stimulation: Seaband® stimulation on a point on the dorsal side of both forearms, four fingers breadth proximal	Women were divided into two groups according to their own description of their susceptibility of motion sickness (low or high) and then randomized

		sickness were included in each group. An eccentrically rotating chair was used to stimulate nausea. The chair rotation speed was 60°/s. The nauseogenic motion was a combination of head movements (chin to chest head flexion) while the subject was blindfolded and seated on the chair rotating eccentrically about a vertical axis.	to the proximal flexor palmar crease. 3. Control group: no wristband.	to one of three study groups.
Bertolucci, 1995, USA	Experimental: Randomized controlled trial	5 men and 4 women, ages 39-53, who were passenger aboard a 50-foot commercial boat on a day trip to observe sea life.	1. Active acustimulation: ReliefBand® positioned on the palmar surface of either the right or left wrist, near the median nerve, and approximately 5 cm proximal to the most proximal crease of the flexed wrist (P6 point). 2. Placebo stimulation: ReliefBand® positioned on the posterior surface of the wrist.	In 4 subjects the device was switched from the active P6 stimulation to the placebo stimulation site on the posterior surface of the wrist by the investigator. In 5 other subjects, the device was initially worn in the posterior position for placebo stimulation for 1 h and then switched to the anterior wrist position for stimulation over the P6 point.
Estrada, 2007, USA	Experimental: Randomized controlled trial (within subjects design)	64 male (18-34 years), non-aviator subjects. Helicopter flight experience was limited to less than 10 h. The helicopter flight lasted approximately 30 minutes. 16 subjects were randomly assigned to each of four countermeasure groups. Each individual participated once with the active countermeasure and once with a placebo, each flight scheduled 7 d apart.	1. Promethazine + caffeine vs placebo 2. Meclizine vs placebo 3. Scopolamine vs placebo 4. Acustimulation wristband (ReliefBand®) vs placebo. The underside of the ReliefBand® has a pair of gold-plated electrodes that contact the skin. It has 5 levels of intensity. It is worn like a watch at the underside of the wrist. For the placebo, the band is worn with the stimulus producing side on the back of the wrist, away from the median nerve point (P6).	

			[only data on the acustimulation wristband was extracted]	
Hu, 1995, USA	Experimental: Randomized controlled trial	64 undergraduate students (32 men, 32 women), age range 18-25 years. Subjects sat in an optokinetic drum for 24 min: 12 min baseline and 12 min drum rotation. The drum rotation speed was 60°/s for all groups.	1. P6 acupressure: manual pulse pressure with about 1 pulse per second at the left P6 acupuncture point. 2. Dummy-point acupressure: manual pulse pressure at a dummy point. 3. Sham acupressure: manual finger contact at P6 but no pulse pressure from the experimenter. 4. Control group: no acupressure. n = 16 in each group.	P6 is located about 3 cm from the distant palmer crease, between the palmaris longus and flexor carpi radialis tendons. Subjective symptoms of motion sickness (SSMS) were obtained by asking subjects to report any discomfort they felt during the drum rotation period immediately after the drum rotation was stopped.
Miller, 2004, USA	Experimental: Randomized controlled trial	77 undergraduates, 19 men and 61 women, aged 18-27 years who were susceptible to motion sickness. Subjects sat on a stool with their head positioned directly underneath an optokinetic projection drum with a random pattern of various sized dots and a point light source that was suspended from the ceiling. The drum rotated around its vertical axis at a speed of 10 rpm.	1. Acuband™: Acupressure device consisting of a wristband with a ball on it that could be pressed into the P6 point. Untrained (n=17) / Trained (n=23) 2. Reliefband®: Acustimulation device with two electrodes generating a maximum reacting biphasic waveform output of 0.35 mA. Untrained (n=15) / Trained (n=25) 3. Placebo (n=15): an oblong, unique-looking Advanced Healing Band-Aid™ that was placed on the top side of the hand.	The placebo patched was presented to the subjects as being a transdermal patch that released an experimental motion sickness medicine through their skin.
Stern, 2001, USA	Experimental: Randomized controlled trial	25 healthy subjects, 15 female and 10 male, aged 18-22 years, all Pennsylvania State University students. Subjects were susceptible to vection-induced motion sickness and were not familiar with Acubands. Subjects sat on a stool in the optokinetic drum	1. Acuband on the wrist: between the 2 tendons on the wrist and 3 fingers widths up from the crease. 2. Acuband on the arm: 3 finger widths down from the elbow crease on the top side of the forearm. 3. Control: No Acuband	Subjects were told to apply circular pressure on the button of the Acuband as soon as they began to experience any symptoms.

		which had alternating black and white vertical stripes on the inner surface. The drum rotated at a speed of 10 revolutions/min for 16 minutes or until the subject requested that it be stopped.	[only data from Acuband on the wrist were extracted]	
Warwick-Evans, 1991, UK	Experimental: Randomized controlled trial	36 male undergraduates, mean age 21.3 years (range 18-25) at Southampton University. Matched pairs design was chosen. Matching was on the basis of scores on Reason's Motion Sickness Questionnaire. Subjects were split into 2 equal groups according to their high or low susceptibility to motion sickness: n=18 in each group. The nauseogenic situation involved subjects being rotated in a chair about their vertical axis at 8 revolutions/min, while tilting head and trunk 45° alternately to the left or right once every 4 seconds. Each subject was exposed to this situation for 10 minutes.	1. Acupressure: complete SeaBand correctly positioned on the P6 point. 2. Placebo: pressure source of the SeaBand was removed and the band was placed 5 cm away from the P6 point and towards the elbow.	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Time to moderate nausea (sec)	P6 acupressure vs placebo acupressure	Not statistically significant: 352±198.7 vs 280±254.3 MD: 72.0, 95%CI [-69.4; 213.4] (p=0.32)* ¥	1, 20 vs 20 §	Alkaissi, 2005
	P6 acupressure vs control	Statistically significant: 352±198.7 vs 151±64.1 MD: 201.0, 95%CI [109.5; 292.5] (p<0.0001)* *In favour of P6 acupressure*		
SSMS	Active P6 stimulation vs placebo stimulation	Statistically significant: 1.0±0.07 vs 4.0±1.4 MD: -3.00, 95%CI [-4.37; -1.63] (p<0.001)* *In favour of active P6 stimulation*	1, 5 vs 4 §	Bertolucci, 1995
Symptom severity	P6 acupressure wristband vs placebo	Not statistically significant: 29±6 vs 31±7.5 MD: -2.0 (p>0.05) λ£†	1, 16 vs 16 § (within subjects design)	Estrada, 2007

SSMS (mean±SEM)	P6 acupressure vs dummy point acupressure	Statistically significant: 5.56±0.89 vs 8.81±1.34 MD: -3.25, 95%CI [-6.40; -0.10] (p=0.04)* *In favour of P6 acupressure*	1, 16 s 16 §	Hu, 1995
	P6 acupressure vs sham point acupressure	Statistically significant: 5.56±0.89 vs 11.06±1.61 MD: -5.50, 95%CI [-6.40; -4.60] (p<0.00001)* *In favour of P6 acupressure*		
	P6 acupressure vs control	Statistically significant: 5.56±0.89 vs 11.25±1.67 MD: -5.69, 95%CI [-6.62; -4.76] (p<0.00001)* *In favour of P6 acupressure*		
SSMS	P6 acupressure vs placebo	Not statistically significant: 7.889 vs 6.889 ££ MD: 1.0 (p>0.05) £†	1, 18 vs 18 §	Warwick-Evans, 1991
Peak total symptoms score	ReliefBand™ Untrained vs placebo	Not statistically significant: 66.5±26.5 vs 76.1±42.1 MD: -9.60, 95%CI [-34.775; 15.57] (p=0.45)*	1, 15 vs 15 §	Miller, 2004
	ReliefBand™ Trained vs placebo	Not statistically significant: 76.1±76.1 vs 76.1±42.1 MD: 0.00, 95%CI [-36.66; 36.66] (p=1.00)*	1, 25 vs 15 §	
	AcuBand™ Untrained vs placebo	Not statistically significant: 85.5±36.9 vs 76.1±42.1 MD: 9.40, 95%CI [-18.20; 37.00] (p=0.50)*	1, 17 vs 15 §	
	ReliefBand™ Trained vs placebo	Not statistically significant: 67.2±38.7 vs 76.1±42.1 MD: -8.90, 95%CI [-35.43; 17.63] (p=0.51)*	1, 25 vs 15 §	
Mean report of motion sickness symptoms	Acuband-arm vs control	Statistically significant: 7.8 vs 11.9 ££ MD: -4.1 (p<0.01) £ *In favour of Acuband-arm*	1, 25 vs 25 § (within subjects design)	Stern, 2001
Nausea	P6 acupressure wristband vs placebo	Not statistically significant: 25±5 vs 25.5±0.55 MD: -0.5 (p>0.05) £†	1, 16 vs 16 § (within subjects design)	Estrada, 2007

Mean ± SD (unless otherwise indicated)
* Calculations done by the reviewer(s) using Review Manager software
£ No CI available
££ No SD's available
† Imprecision (lack of data)
§ Imprecision (limited sample size)
¥ Imprecision (large variability of results)
λ Data extracted from graph

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Alkaissa, 2005	No, sealed envelope	No, only in control group, but there was	No	No	

		also a placebo group included			
Bertolucci, 1995	Unclear, not mentioned	No, subjects were unaware of differences in the sites of stimulation. A third party was used to instruct subjects on the use of the device.	No	Yes, initially 21 subjects entered the study, but only data of 9 subjects is reported.	
Estrada, 2007	Unclear, randomized into 4 groups, but not mentioned how	No, participants were kept unaware of their countermeasure group or order.	No	No	Within subjects
Hu, 1995	Unclear, randomly divided into 4 groups, but not mentioned how	Unclear	No	No	
Miller, 2004	No, cards drawn from a bag	No, placebo group was told the Band-Aid released an experimental medicine through their skin	No	No	
Stern, 2001	Unclear, randomly assigned, but not mentioned how	Yes, control subjects did not have a band.	No	No	supported by a grant from the AcuBand company.
Warwick-Evans, 1991	Unclear, randomized but not mentioned how	No, the experimenter who recorded the data did not know which placement was used.	No	No	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/lack of data/large variability of the results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [D]**	

Conclusion	There is limited evidence in favour of P6 acupressure or P6 acustimulation. In making this evidence conclusion, we place a higher value on the outcome "subjective symptoms of motion sickness" (SSMS) over "peak total symptoms score" or nausea (only one of many symptoms of motion sickness. It was shown that P6 acupressure or P6 stimulation resulted in a statistically significant decrease of SSMS, compared to control, sham point acupressure or dummy point acupressure or placebo (Bertolucci 1995, Hu 1995, Stern 2001). Furthermore, it was shown that P6 acupressure resulted in a statistically significant increase of time to moderate nausea, compared to control (Alkaissi 2005).

	However, a statistically significant decrease of symptom severity, peak total symptoms score, SSMS or nausea, using P6 acupressure or P6 acustimulation compared to placebo, could not be demonstrated (Estrada 2007, Miller 2004, Warwick-Evans 1991). Evidence is of low quality and results cannot be considered precise due to limited sample size, lack of data and/or large variability of results.
Reference(s)	**Articles** Alkaisi A, Ledin T, Odkvist LM, Kalman S. *P6 acupressure increases tolerance to nauseogenic motion stimulation in women at high risk for PONV*. Can J Anesth 2005, 52(7):709-709 Bertolucci LE, DiDario B. *Efficacy of a Portable Acustimulation Device in Controlling Seasickness*. Aviat Space Environ Med 1995, 66(12):1155-8 Estrada A, LeDuc PA, Curry IP, Phelps SE, Fuller DR. *Airsickness prevention in helicopter passengers*. Aviat Space Environ Med 2007, 78(4) section I: 408-413 Hu S, Stritzel R, Chandler A, Stern RM. *P6 acupressure reduces symptoms of vection-induced motion sickness*. Aviat Space Environ Med 1995, 66(7):631-634 Miller KE, Muth ER. *Efficacy of Acupressure and Acustimulation Bands for the Prevention of Motion Sickness*. Aviat Space Environ Med 2004, 75(3):227-234 Stern RM, Jokerst MD, Muth ER, Hollis C. *Acupressure relieves the symptoms of motion sickness and reduces abnormal gastric activity*. Altern Ther Health Med 2001, 7(4):91-94 Warwick-Evans LA, Redstone SB. *A Double-Blind Placebo Controlled Evaluation of Acupressure in the Treatment of Motion Sickness*. Aviat Space Environ Med 1991, 62:776-8

Embolism/Deep vein thrombosis – Exercise (Prevention)

Question (PICO)	In humans who need to sit a long time with limited leg space (P), is doing exercises with the legs (I) compared to not doing this (C) effective to prevent embolism (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 4. [mh "Embolism and Thrombosis"] OR embolism:ti,ab,kw 5. [mh "Travel"] OR [mh "Aircraft"] OR travel:ti,ab,kw OR air:ti,ab,kw OR sitting:ti,ab,kw OR seat*:ti,ab,kw 6. [mh "Stockings, compression"] OR (compression:ti,ab,kw AND stocking*:ti,ab,kw) OR [mh "Fluid Therapy"] OR drink*:ti,ab,kw OR [mh "Drinking"] OR [mh "Exercise"] OR exercise*:ti,ab,kw OR [mh "Clothing"] OR cloth*:ti,ab,kw 7. 1-3 AND **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Embolism and Thrombosis"[Mesh] OR embolism[TIAB] 2. "Travel" [Mesh] OR "Aircraft"[Mesh] OR travel[TIAB] OR air[TIAB] OR sitting[TIAB] OR seat*[TIAB] 3. "Stockings, compression"[Mesh] OR (compression[TIAB] AND stocking*[TIAB]) OR "Fluid Therapy"[Mesh] OR drink*[TIAB] OR "Drinking"[Mesh] OR "Exercise"[Mesh] OR exercise*[TIAB] OR "Clothing"[Mesh] OR cloth*[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'thromboembolism'/exp OR embolism:ab,ti 2. 'travel'/exp OR 'aircraft'/exp OR travel:ab,ti OR air:ab,ti OR sitting:ab,ti OR seat*:ab,ti 3. 'compression stocking'/exp OR (compression:ab,ti AND stocking*:ab,ti) OR 'fluid therapy'/exp OR drink*:ab,ti OR 'drinking'/exp OR 'exercise'/exp OR exercise*:ab,ti OR 'clothing'/exp OR cloth*:ab,ti

	4. 1-3 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	2 October 2015
In/Exclusion criteria	**Population**: Include: adults or children who need to sit down for long times with limited leg space (e.g. long travelling times) **Intervention**: Include: exercising with legs **Comparison**: Include: not doing this **Outcome**: Include: prevention of embolism, deep vein thrombosis **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclusion if experimental studies were already included. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Caruana, 2003, UK	Experimental: Non-randomized controlled trial (within subjects design)	15 healthy volunteers	Intervention: calf muscle pump exercises with a dynamic alternating inflatable biped device (Lymgym, Lymgym Ltd, UK) Control: seated position	Doppler ultrasound was used to assess peak flow velocity in the superficial femoral vein in the lower limbs.
Hitos, 2007, Australia	Experimental: Randomized controlled trial (within subjects design)	21 healthy subjects Subjects remained seated throughout the investigation and 3660 duplex ultrasound examinations were performed by a single examiner using a SonoSite 180 Plus handheld ultrasound.	Interventions: Airline recommended activities, foot exercises, foot exercises against moderate resistance, foot exercises against increased resistance, sitting with feet not touching the floor Control: sitting still with feet touching the flour	In the foot exercise against moderate resistance, active plantar and dorsiflexion foot exercises were performed on a flat, non-pivoting springboard obtained from an armchair. In the foot exercise against increased resistance, an apparatus was designed that consisted of a pivoting pedal

				connected with an elastic tension band. This allowed subjects to perform active plantar and dorsiflexion exercises requiring increased muscle exertion.
Stein, 2009, USA	Experimental: non-randomized controlled trial	20 healthy male volunteers	Intervention: ankle exercise Control: rest Both conditions were tested in supine and sitting position.	Time-averaged peak velocity (TAPV) in the popliteal vein was measured by pulsed Doppler ultrasound. Ankle exercise: the subject maximally dorsiflexed and plantarflexed his right foot at an average rate of 62 flexions/min

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Percentage change in blood volume flow from baseline after 100 min	Airline recommended activities vs sitting still	Statistically significant: -17 vs -42 £ (p=0.0024) *In favour of airline recommended activities*	1, 21 vs 21 § (within subjects design)	Hitos, 2007
Percentage change in blood volume flow from baseline after 100 min	Foot exercises vs sitting still	Statistically significant: -16 vs -42 £ (p=0.0024) *In favour of foot exercises*		
Popliteal vein cross-sectional area		Statistically significant: MD: -14 £ (p<0.0001) *In favour of foot exercises*		
Percentage change in blood volume flow from baseline after 100 min	Foot exercises against increased resistance vs sitting still	Statistically significant: 2.2 vs -42 £ (p<0.0001) *In favour of foot exercises against increased resistance*		
Popliteal vein cross-sectional area		Statistically significant: MD: -5.9 £ (p=0.0014) *In favour of foot exercises against increased resistance*		
Percentage change in blood volume flow from baseline after 100 min	Foot exercises against moderate resistance vs sitting still	Statistically significant: 5.8 vs -42 £ (p<0.0001) *In favour of foot exercises against moderate resistance*		
Differences in the popliteal vein cross-sectional area		Statistically significant: MD: -25 £ (p<0.0001) *In favour of foot exercises against moderate resistance*		

Percentage change in blood volume flow from baseline after 65 min	Sitting still with feet not touching the floor vs sitting still	Statistically significant: -48 vs -29 £† (p=0.015) *In favour of sitting still with feet touching the floor*		
Right popliteal vein time-averaged peak velocity (cm/sec)	Supine: Ankle exercise vs rest	Statistically significant: 24 vs 11 £ (p<0.0001) *In favour of ankle exercise*	1, 20 vs 20 § (within subjects design)	Stein, 2009
	Sitting: Ankle exercise vs rest	Statistically significant: 18 vs 3 £ (p<0.0001) *In favour of ankle exercise*		
Peak blood flow velocity	Exercises with biped device vs sitting	Statistically significant: On starting exercise: (Median, Interquartile range): 0.88 (0.84-0.98) vs 0.11 (0.09-0.14) ££ After 5 strokes: 0.41 (0.36-0.48) vs 0.11 (0.09-0.14) ££ *In favour of exercises with biped device*	1, 15 vs 15 § (within subjects design)	Caruana, 2003

£ No raw data/SD's/CI available
££ No effect size and CI available
§ Imprecision (limited sample size)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Caruana, 2003	Yes (no randomization)	Unclear	No	No	within subjects design
Hitos, 2007	Unclear (method of random assignment unclear)	No (the examiner was blinded to the exercise regimen performed)	No	No	within subjects design
Stein, 2009	Yes (no randomization)	Yes	No	No	within subjects design

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Low number of participants
Inconsistency	0	
Indirectness	-1	Indirect population, outcomes
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Conclusion(s)	There is limited evidence in favour of exercises. It was shown that airline recommended activities, foot exercises, sitting still with feet touching the floor, ankle exercises and exercises with a biped device resulted in a statistically significant higher blood volume flow, decrease of popliteal vein cross-sectional area, increase in blood flow velocity compared to sitting still (Caruana 2003, Hitos 2007, Stein 2009). Evidence is of very low quality and results cannot be considered precise due to limited sample size or lack of data.
Reference(s)	**Articles**

	Caruana MF, Brightwell RE, Huguet EL, Whitear P, Hodgkinson DW, Osman IS. *Calf exercise in the seated position using a new dynamic biped device increases femoral vein peak velocity up to eight-fold*. ***Phlebology*** 2003, **18:2** (70-72) Hitos K, Cannon M, Cannon S, Garth S, Fletcher JP. *Effect of leg exercises on popliteal venous blood flow during prolonged immobility of seated subjects: implications for prevention of travel-related deep vein thrombosis*. J Thromb Haemost 2007, 5(9):1890-5 Stein PD, Yaekoub AY, Ahsan ST, Matta F, Lala MM, Mirza B, Badshah A, Zamlut M, Malloy DJ, Denier JE. *Ankle exercise and venous blood velocity*. Thromb Haemost 2009, 101(6):1100-3

Embolism/Deep vein thrombosis – Compression stockings (Prevention)

Question (PICO)	In humans who need to sit a long time with limited leg space (P), is wearing compression stockings (I) compared to not doing this (C) effective to prevent embolism/deep vein thrombosis (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Embolism and Thrombosis"] OR embolism:ti,ab,kw 2. [mh "Travel"] OR [mh "Aircraft"] OR travel:ti,ab,kw OR air:ti,ab,kw OR sitting:ti,ab,kw OR seat*:ti,ab,kw 3. [mh "Stockings, compression"] OR (compression:ti,ab,kw AND stocking*:ti,ab,kw) OR [mh "Fluid Therapy"] OR drink*:ti,ab,kw OR [mh "Drinking"] OR [mh "Exercise"] OR exercise*:ti,ab,kw OR [mh "Clothing"] OR cloth*:ti,ab,kw 4. 1-3 AND **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Embolism and Thrombosis"[Mesh] OR embolism[TIAB] 2. "Travel" [Mesh] OR "Aircraft"[Mesh] OR travel[TIAB] OR air[TIAB] OR sitting[TIAB] OR seat*[TIAB] 3. "Stockings, compression"[Mesh] OR (compression[TIAB] AND stocking*[TIAB]) OR "Fluid Therapy"[Mesh] OR drink*[TIAB] OR "Drinking"[Mesh] OR "Exercise"[Mesh] OR exercise*[TIAB] OR "Clothing"[Mesh] OR cloth*[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'thromboembolism'/exp OR embolism:ab,ti 2. 'travel'/exp OR 'aircraft'/exp OR travel:ab,ti OR air:ab,ti OR sitting:ab,ti OR seat*:ab,ti 3. 'compression stocking'/exp OR (compression:ab,ti AND stocking*:ab,ti) OR 'fluid therapy'/exp OR drink*:ab,ti OR 'drinking'/exp OR 'exercise'/exp OR exercise*:ab,ti OR 'clothing'/exp OR cloth*:ab,ti 4. 1-3 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	2 October 2015
In/Exclusion criteria	**Population**: Include: adults or children who need to sit down for long times with limited leg space (e.g. long travelling times) **Intervention**: Include: wearing compression stockings **Comparison**: Include: not doing this **Outcome**: Include: prevention of embolism, deep vein thrombosis

	Design: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years Remark: The systematic reviews by Kuipers et al. 2007, Philbrick et al. 2007 and Hsieh et al. 2005 are all covered by the Cochrane systematic review.

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Clarke, 2006, UK	Systematic review	9 Randomized Controlled Trials were included in the systematic review (Cochrane review) (n=2821). Seven of the trials recruited a total of 1548 participants who were judged to be of low or medium risk of a deep vein thrombosis (DVT) and two included high risk participants. All flights lasted at least seven hours.	Ten randomized trials (n = 2856) were included; nine (n = 2821) compared wearing stockings on both legs versus not wearing them, and one (n = 35) compared wearing a stocking on one leg for the outbound flight and on the other leg on the return flight.	Review content assessed as up-to-date: 3 April 2007 All the trials assessed incidence of symptomless DVT within a few days of the flight. Symptomless DVT was assessed by ultrasound or D-dimer testing and fibrinogen tests.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Symptomless deep vein thrombosis	Wearing stockings on both legs vs not wearing them	Statistically significant: 3/1314 vs 47/1323 § OR: 0.10, 95%CI [0.04;0.25] (p<0.00001) *In favour of wearing stockings*	9, 1314 vs 1323	Clarke, 2006
Superficial vein thrombosis	Wearing stockings on both legs vs not wearing them	Not statistically significant: 4/903 vs 12/901 § OR: 0.45, 95%CI [0.18;1.13] (p=0.089) ¥	8, 903 vs 901	Clarke, 2006

§ Imprecision (low number of events)

¥ Imprecision (large variability of results)

Quality of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See systematic review Clarke 2006
Imprecision	-1	Low number of events/large variability of results (for one outcome)
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion(s)	There is limited evidence in favour of wearing stockings. It was shown that wearing stockings resulted in a statistically significant decrease of symptomless deep vein thrombosis, compared to not wearing stockings (Clarke 2006). A statistically significant decrease of superficial vein thrombosis wearing stockings compared to not doing this could not be demonstrated (Clarke 2006). Evidence is of low quality and results cannot be considered precise due to low number of events and/or large variability of results.
Reference(s)	**Articles** Clarke M, Hopewell S, Juszczak E, Eisinga A, Kjeldstrøm M. *Compression stockings for preventing deep vein thrombosis in airline passengers*. Cochrane Database Syst Rev 2006, (2):CD004002

Embolism/Deep vein thrombosis – Risk factors

Question (PICO)	In humans who need to sit a long time with limited leg space (P), which are risk factors (RF) for embolism/deep vein thrombosis (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Embolism and Thrombosis"] OR embolism:ti,ab,kw 2. [mh "Travel"] OR [mh "Aircraft"] OR travel:ti,ab,kw OR air:ti,ab,kw OR sitting:ti,ab,kw OR seat*:ti,ab,kw 3. [mh "Stockings, compression"] OR (compression:ti,ab,kw AND stocking*:ti,ab,kw) OR [mh "Fluid Therapy"] OR drink*:ti,ab,kw OR [mh "Drinking"] OR [mh "Exercise"] OR exercise*:ti,ab,kw OR [mh "Clothing"] OR cloth*:ti,ab,kw 4. 1-3 AND **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Embolism and Thrombosis"[Mesh] OR embolism[TIAB] 2. "Travel" [Mesh] OR "Aircraft"[Mesh] OR travel[TIAB] OR air[TIAB] OR sitting[TIAB] OR seat*[TIAB] 3. "Stockings, compression"[Mesh] OR (compression[TIAB] AND stocking*[TIAB]) OR "Fluid Therapy"[Mesh] OR drink*[TIAB] OR "Drinking"[Mesh] OR "Exercise"[Mesh] OR exercise*[TIAB] OR "Clothing"[Mesh] OR cloth*[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'thromboembolism'/exp OR embolism:ab,ti 2. 'travel'/exp OR 'aircraft'/exp OR travel:ab,ti OR air:ab,ti OR sitting:ab,ti OR seat*:ab,ti 3. 'compression stocking'/exp OR (compression:ab,ti AND stocking*:ab,ti) OR 'fluid therapy'/exp OR drink*:ab,ti OR 'drinking'/exp OR 'exercise'/exp OR exercise*:ab,ti OR 'clothing'/exp OR cloth*:ab,ti 4. 1-3 AND

	Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in MEDLINE (via PubMed interface).
Search date	2 October 2015
In/Exclusion criteria	**Population**: Include: adults or children who need to sit down for long times with limited leg space (e.g. long travelling times) **Intervention**: Include: modifiable, proximal risk factor with a potential immediate implication for practice that results in primary prevention at the household or community level. Risk factors related to healthy persons. Exclude: Risk factors concerning exercises or wearing stockings (since these are dealt with in a separate PICO question); risk factors that lead to interventions with already proven effectiveness. The risk factor that does not precede the outcome. The risk factor is common sense. **Outcome**: Include: prevention of embolism, deep vein thrombosis **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Risk factor	Remarks
Schreijer, 2009, The Netherlands	Observational: case-control study	Cases: 80 patients who had recently (<8 weeks) travelled for more than 4 h by airplane Controls: 108 control subjects who had recently (<8 weeks) travelled for more than 4 h by airplane; control subjects were partners of patients or recruited using a random digit dialling method	Multiple risk factors for venous thrombosis, including recent travel history and details of their last flight [only data concerning eligible risk factors were extracted (see selection criteria)]	All ORs were adjusted for age, sex (except for oral contraceptive use) and, when applicable, for duration of the flight and the presence of varicose veins.

Synthesis of findings

Outcome	Risk factor	Effect Size	#studies, # participants	Reference
Risk of venous thrombosis	Window seat vs aisle seat	Statistically significant: OR: 2.2, 95%CI [1.1;4.4] (p<0.05) £ *In favour of aisle seat*	1, 80 vs 108 §	Schreijer, 2009
	Middle seat vs aisle seat	Not statistically significant:		

		OR: 1.1, 95% CI [0.5;2.5] (p>0.05) £¥		
	1 glass of alcohol vs no alcohol	Not statistically significant: OR: 0.5, 95%CI [0.2,1.2] (p>0.05) £¥		
	2 or more glasses of alcohol vs not alcohol	Not statistically significant: OR: 1.1, 95%CI [0.5;2.4] (p>0.05) £¥		
	Sleeping during flight vs not	Not statistically significant: OR: 1.5, 95%CI [0.7;3.1] (p>0.05) £¥		
	Sleep medication vs not	Not statistically significant: OR: 1.2, 95%CI [0.4;3.6] (p>0.05) £¥		
	More than 2 non-alcoholic drinks vs 0-2 drinks	Not statistically significant: OR: 1.2, 95%CI [0.4;4.0] (p>0.05) £¥		

£ No raw data available
§ Imprecision (low number of events)
¥ Imprecision (large variability of results)

Quality of evidence

Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations
Schreijer, 2009	No	No	No	No	

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Low number of events, large variability in results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Conclusion(s)	It was shown that sitting on a window seat resulted in a statistically significant increased risk of venous thrombosis, compared to sitting on an aisle seat (Schreijer 2009). A statistically significant increased risk of venous thrombosis in case of the following risk factors could not be demonstrated: sitting on a middle seat (vs aisle seat, drinking 1 or more glasses of alcohol, sleeping during the flight, taking sleep medication or drinking more than 2 drinks (vs 0 to 2 drinks) (Schreijer 2009). Evidence is of very low quality and results cannot be considered precise due to limited number of events and large variability of results.
Reference(s)	**Articles** Schreijer AJ, Cannegieter SC, Doggen CJ, Rosendaal FR. *The effect of flight-related behaviour on the risk of venous thrombosis after air travel*. Br J Haematol 2009, 144(3):425-9

ALLERGIES

Swollen throat due to insect bite – Ice or cold water (First aid)

Question (PICO)	In humans with a swollen throat due to an insect bite (P), is sucking on ice or cooling the mouth with cold water (I) compared to not doing this (C) effective to reduce the swelling of the throat (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. Throat:ti,ab,kw AND (swelling:ti,ab,kw OR swollen:ti,ab,kw OR angioedema:ti,ab,kw) 2. [mh ice] OR ice:ti,ab,kw OR cold*:ti,ab,kw OR cool*:ti,ab,kw 3. #1 AND #2 **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. throat[TIAB] and (swelling[TIAB] OR swollen[TIAB] OR angioedema[TIAB]) 2. Ice[Mesh] OR ice[TIAB] OR cold*[TIAB] OR cool*[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. throat:ab,ti AND (swelling:ab,ti OR swollen:ab,ti OR angioedema:ab,ti) 2. Ice/exp OR ice:ab,ti OR 'cold water':ab,ti OR cool*:ab,ti 3. 1-2 AND
Search date	01 July 2015
In/Exclusion criteria	**Population:** Include: Healthy adults or children with a swollen throat because of an allergic reaction to an insect bite. Exclude: people with a swollen throat due to other reasons. **Intervention:** Include: sucking on ice cubes, rinsing mouth with cold water, drinking cold water, any intervention to cool the throat. **Comparison:** no intervention or any other intervention such as medication or warm drinks. **Outcome:** Include: Reduction of swelling, pain, dyspnea, time to resolution of symptoms, survival. **Study design:** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

FEVER

Fever - Palpation of the forehead to diagnose fever (First Aid)

Question (PICO)	In people with a fever (P), can palpation of the forehead (I) (versus other temperature measurements (C)) be used to diagnose fever (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "fever"] OR fever:ti,ab,kw OR hypertherm*:ti,ab,kw OR pyrexi*:ti,ab,kw OR "body temperature increase*":ti,ab,kw OR "body temperature elevat*":ti,ab,kw OR "febrile response":ti,ab,kw OR [mh "body temperature"] OR [mh "body temperature changes"] OR "body temperature change*":ti,ab,kw 2. [mh "hand"] OR hand:ti,ab,kw OR hands:ti,ab,kw OR [mh "palpation"] OR [mh "physical examination"] OR [mh "touch"] OR touch*:ti,ab,kw OR tact*:ti,ab,kw OR palpat*:ti,ab,kw 3. [mh "sensitivity and specificity"] OR sensitivity:ti,ab,kw OR specificity:ti,ab,kw OR "pre-test probability":ti,ab,kw OR "pretest probability":ti,ab,kw OR "post-test probability":ti,ab,kw OR "posttest probability":ti,ab,kw OR "predictive value":ti,ab,kw OR "predictive values":ti,ab,kw OR "likelihood ratio":ti,ab,kw OR "likelihood ratios":ti,ab,kw OR [mh "reproducibility of results"] OR reproducibilit*:ti,ab,kw OR reliabilit*:ti,ab,kw 4. 1-3 AND **MEDLINE** (via PubMed interface) for guidelines, systematic reviews, experimental and observational studies using the following search strategy: 1. "Fever"[MeSH] OR fever*[TIAB] OR hypertherm*[TIAB] OR pyrexi*[TIAB] OR body temperature increase*[TIAB] OR body temperature elevat*[TIAB] OR febrile response[TIAB] OR "Body temperature"[MeSH] OR "Body temperature changes"[MeSH] OR body temperature change*[TIAB] 2. "Hand"[MeSH] OR hand[TIAB] OR hands[TIAB] OR "Palpation"[MeSH] OR "physical examination"[MeSH:NoExp] OR touch[MeSH] OR touch*[TIAB] OR tact*[TIAB] OR palpat*[TIAB] 3. "Sensitivity and specificity"[Mesh] OR "Sensitivity"[TIAB] OR "Specificity"[TIAB] OR "Pre-test probability"[TIAB] OR "Pretest probability"[TIAB] OR "Post-test probability"[TIAB] OR "Posttest probability"[TIAB] OR "Predictive value"[TIAB] OR "Predictive values"[TIAB] OR "Likelihood ratio"[TIAB] OR "Likelihood ratios"[TIAB] OR "reproducibility of results"[MeSH] OR reproducibilit*[TIAB] OR reliabilit*[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'Fever'/exp OR fever*:ab,ti OR hypertherm*:ab,ti OR pyrexi*:ab,ti OR (body NEXT/1 temperature NEXT/1 increase*):ab,ti OR (body NEXT/1 temperature NEXT/1 elevat*):ab,ti OR (febrile NEXT/1 response):ab,ti OR 'body temperature'/exp OR (body NEXT/1 temperature NEXT/1 change*):ab,ti 2. 'hand'/exp OR hand:ab,ti OR hands:ab,ti OR 'palpation'/exp OR 'physical examination'/de OR 'touch'/exp OR touch*:ab,ti OR tact*:ab,ti OR palpat*:ab,it 3. 'Diagnostic accuracy'/exp OR 'Sensitivity and specificity'/exp OR 'Sensitivity':ab,ti OR 'Specificity':ab,ti OR ((Pre-test or pretest) near/5 probability):ab,ti OR 'Post-test probability':ab,ti OR 'Posttest probability':ab,ti OR 'Predictive value':ab,ti OR 'Predictive values':ab,ti OR 'Likelihood ratio':ab,ti OR 'Likelihood ratios':ab,ti OR 'reproducibility'/exp OR reproducibilit*:ab,ti OR reliabilit*:ab,ti 4. 1-3 AND

	Guidelines, systematic reviews, retrieved with the above searches, and used as source for individual studies: Teng, 2008 (as source of individual studies with update, as the PICO was limited to the use of palpation by mothers and only 1 database was searched) Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	2nd May 2016
In/Exclusion criteria	**Population:** Include: children or adults with fever. Exclude: children or adults with hypothermia **Intervention:** Include: temperature measurement through palpation (of the forehead) **Comparison:** Include: temperature measurement via other means **Outcome:** Include: Diagnosis of fever (true positives, false positives, true negatives, false negatives), Level of agreement between two methods **Study design:** Include: a systematic review: inclusion of diagnostic studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. If no systematic review of diagnostic studies is present, individual diagnostic studies (randomized controlled trial or diagnostic accuracy study) will be included. **Language**: Include: English, French, German, Dutch **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison/Risk factor	Remarks
Abdulkadir, 2014, Nigeria	Diagnostics: Diagnostic accuracy study	409 children, between 2 and 59 months (mean age 21.86±15.3 months), male:female ratio of 1.6:1, presenting at an emergency paediatric unit with a history of fever in the past 48h, and their caregivers (mean age 30.1±4.54 years)	Index test: Palpation of children by caregivers at an anatomical location of choice Reference standard: Rectal and axillary digital thermometry (U-mec) [data of comparison with axillary thermometry were not extracted, as rectal thermometry is considered to be the gold standard]	A power analysis revealed a necessary n-value of 384
Akinbami, 2010, Nigeria	Diagnostics: Diagnostic accuracy study	182 children, between 6 and 59 months (median age 15), presenting at an emergency paediatric unit, and their caregivers	Index test: Palpation of children by caregivers, doctors or nurses on the head, neck, chest or abdomen Reference standard: Rectal thermometry with a mercury in glass thermometer	
Alves, 2002, Brazil	Diagnostics: Diagnostic accuracy study	169 children, between 2 months and 13 years (mean age 31±21 months), 94 male and 75 female, presenting at an emergency paediatric unit, and their mothers	Index test: Palpation of children by their mothers in the neck Reference standard: Axillary thermometry with a mercury glass thermometer	

Asekun-Olarinmoye, 2009, Nigeria	Diagnostics: Diagnostic accuracy study	300 children, between 1 month and 12 years (mean age 22.22±20.95 months), 148 male and 152 female, presenting at 4 randomly selected primary health care centres in Osogbo, and their mothers, mean age 27.7±6.7 years	Index test: Palpation of children by their mothers at an anatomical location of choice Reference standard: Axillary thermometry with a mercury glass thermometer	A power analysis revealed a necessary n-value of 302
Bergeson, 1974, USA	Diagnostics: Diagnostic accuracy study	1149 children, between newborn and 18 years old, presenting at an emergency paediatric unit	Index test: Palpation of children by nurses at an anatomical location of choice Reference standard: Oral thermometry (> 3.5 years and not tachypneic) and rectal thermometry (< 3.5 years)	Comparison was made between "no fever vs low fever vs high fever", but this was extracted as "no fever vs fever" to be able to calculate LRs
Callanan, 2003, USA	Diagnostics: Diagnostic accuracy study	179 children, < 3 months, presenting at an emergency paediatric unit, and their caregiver	Index test: Palpation of children by caregiver at an anatomical location of choice Reference standard: Rectal digital thermometry (WelchAllyn SureTemp)	
Chaturvedi, 2003, India	Diagnostics: Diagnostic accuracy study	200 children, presenting at an emergency paediatric unit, subdivided into 2 groups, and their caregivers: Group 1 (n=100): Infants between 0-1 year Group 2 (n=100): Children between 6-12 years	Index test: Palpation of children by caregiver at an anatomical location of choice and palpation of children by medical staff (doctor or nurse) at forehead, neck, chest and abdomen Reference standard: Rectal mercury glass thermometry for group 1 and oral mercury glass thermometry for group 2	
Clough, 2007, Malawi	Diagnostics: Diagnostic accuracy study	220 patients presenting at a hospital, including 77 children	Index test: Palpation of children by medical staff at an unspecified anatomical location Reference standard: Axillary mercury glass thermometry	
Hooker, 1996, USA	Diagnostics: Diagnostic accuracy study	180 children, < 5 years, mean age 14.6±11.8 months, 101 males and 79 females, presenting at an emergency paediatric unit, and their parents	Index test: Palpation by parents at an anatomical location of choice Non-contact tympanic thermometry	

			Reference standard: Rectal mercury glass thermometry [Data from non-contact tympanic thermometry was not extracted]	
Hung, 2000, USA	Diagnostics: Diagnostic accuracy study, case-control design	64 patients, cases examined for fever and controls with other conditions, recruited from the emergency department and hospital ward, >18 years, and 95 observing clinicians. Cases: 98 observations (mean age 45.1±12.1 years, 64 males and 34 females) Controls: 103 observations (mean age 42.6±19.3, 41 males and 62 females)	Index test: Palpation by clinician at an anatomical location of choice Reference standard: Rectal digital thermometry (FILCH, model F-1010 temperature monitor)	For some patients, multiple comparisons were made by different clinicians, leading to 64 patients being examined by 95 clinicians, resulting in a total of 201 observations [Other data concerning the clinical assessment of jaundice and anaemia was not extracted]
Katz-Sidlow, 2009, USA	Diagnostics: Diagnostic accuracy study	96 children, < 3 months, aged 6-88 days, presenting at an emergency department, and their parents	Index test: Palpation by parents at an anatomical location of choice Reference standard: Rectal digital thermometry (Dinamap Pro 400 V2 Or IVAC turbo temp)	Analysed twice, once with patients who had temperature measured at home included, and once with these patients excluded
Nwanyanwu, 1997, Malawi	Diagnostics: Diagnostic accuracy study	1120 children, <5 years, mean age 18 months (median 15,6), presenting at the outpatient clinic of one of two hospitals. Children were randomly selected (one in four at one site and two in three in the other)	Index test: Palpation of the forehead by the mother or clinical officer Reference standard: Rectal thermometry	
Odinaka, 2014, Nigeria	Diagnostics: Diagnostic accuracy study	113 children, <5 years, aged 2 days to 59 months, male:female ratio of 1.1:1, presenting at the outpatient clinic and emergency	Index test: Palpation by the mother at anatomical locations of choice Reference standard:	

		department, and their mothers	Axillary mercury glass thermometry	
Okposio, 2012, Nigeria	Diagnostics: Diagnostic accuracy study	511 children, aged 6 months to five years, mean age of the selected children 18.9±1.4 months, 213 males and 146 females, presenting at the paediatric emergency unit, and their mothers	Index test: Palpation by the mother at anatomical locations of choice Reference standard: Axillary mercury glass thermometry	
Singh, 2003, India	Diagnostics: Diagnostic accuracy study	462 patients, >13 years, mean age 36.3±15.4 years, 274 male and 188 female, presenting at two inpatient ward and one outpatient department, and their attendants	Index test: Palpation by the attendant or doctor at anatomical locations of choice Reference standard: Axillary mercury glass thermometry	Ability of the attendant to detect fever was also separately analysed for location of palpation in forehead, neck, chest, abdomen, arm and more than 1 area [Only data from forehead was extracted]
Singhi, 1990, India	Diagnostics: Diagnostic accuracy study	301 children, aged 3 months to 12 years, presenting at the outpatient emergency department between 9 AM and 1 PM, and their mothers.	Index test: Palpation by the mother at an anatomical location of choice Reference standard: Axillary mercury glass thermometry <5 years Oral mercury glass thermometry >5 years	Ability of the attendant to detect fever was also separately analysed for location of palpation in forehead, face, neck, abdomen and more than 1 area [Only data from forehead was extracted]
Wammanda, 2009, Nigeria	Diagnostics: Diagnostic accuracy study	126 children, aged 2 months to 59 months, presenting at a paediatric outpatient department on weekdays during shifts of the author, and their mothers	Index test: Palpation of the forehead by the mother Reference standard: Axillary mercury glass thermometry	
Whybrew, 1998, UK	Diagnostics: Diagnostic accuracy study	1090 children, aged 1 month to 16 years, presenting at a hospital in Zambia, and their mothers	Index test: Palpation of the forehead, neck and abdomen by the mother and a medical student Reference standard: Axillary mercury glass thermometry	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Palpation vs rectal thermometry				
Fever (rectal temperature ≥ 38 °C)	Caregiver's touch vs rectal thermometry	LR+: 1.37 LR-: 0.69 Sensitivity: 0.63, 95% CI [0.58;0.68] * Specificity: 0.54, 95% CI [0.41;0.67] * TP: 218/409 FP: 29/409 TN:34/409 FN: 128/409 *index test can be considered as not clinically helpful for the presence of fever*	1, 409 (diagnostic accuracy study)	Abdulkadir, 2014
		LR+: 4.33 ** LR-: 0.11 ** Sensitivity: 0.91, 95% CI [0.72;0.99] * Specificity: 0.79, 95% CI [0.72;0.85] * TP: 21/179 FP: 33/179 *** TN:124/179 *** FN: 2/179 *** *index test can be considered as clinically helpful for the presence of fever*	1, 179 (diagnostic accuracy study)	Callanan, 2003
		LR+: 1.23 ** LR-: 0.62 ** Sensitivity: 0.95, 95% CI [0.91;0.97] Specificity: 0.23, 95% CI [0.17;0.27] TP: 106/182 FP: 54/182 TN: 16/182 FN: 6/182 *index test can be considered as not clinically helpful for the presence of fever*	1, 182 (diagnostic accuracy study)	Akinbami, 2010
		LR+: 3.48 ** LR-: 0.24 ** Sensitivity: 0.82 ££ Specificity: 0.77 ££ TP: £ FP: £ TN: £ FN: £ *index test can be considered as clinically helpful for the presence of fever*	1, 180 (diagnostic accuracy study)	Hooker, 1996
		LR+: 4.52 ** LR-: 0.23 ** Sensitivity: 0.81, 95%CI [0.64;0.98] Specificity: 0.82, 95%CI [0.73;0.91]	1, 88 (diagnostic accuracy study)	Katz-Sidlow, 2009

		TP: 17/88 FP: 12/88 TN: 55/88 FN: 4/88 *index test can be considered as clinically helpful for the presence of fever*		
		LR+: 4.19 ** LR-: 0.39 ** Sensitivity: 0.67, 95%CI [0.23;1.04] Specificity: 0.84, 95%CI [0.74;0.94] TP: 4/? £ FP: 8/? £ TN: £ FN: £ *index test can be considered as clinically helpful for the presence of fever*	1, ? (diagnostic accuracy study)	
		LR+: 1.25 ** LR-: 0.61 ** Sensitivity: 0.76, 95% CI [0.56;0.90] Specificity: 0.39, 95% CI [0.28;0.52] TP: 22/100 FP: 43/100 TN: 28/100 FN: 7/100 *index test can be considered as not clinically helpful for the presence of fever*	1, 100 (diagnostic accuracy study)	Chaturvedi, 2003
	Medical staff's touch vs rectal thermometry	LR+: 2.07 ** LR-: 0.38 ** Sensitivity: 0.76, 95% CI [0.56;0.90] * Specificity: 0.63, 95% CI [0.51;0.75] * TP: 22/100 FP: 26/100 TN: 45/100 FN: 7/100 *index test can be considered as clinically helpful for the presence of fever*		
		LR+: 2.55 ** LR-: 0.26 ** Sensitivity: 0.82, 95% CI [0.78;0.86] * Specificity: 0.68, 95% CI [0.64;0.71] * TP: 337/1118 FP: 228/1118 TN: 480/1118 FN: 73/1118 *index test can be considered as clinically helpful for the presence of fever*	1, 1118 (diagnostic accuracy study)	Nwanyanwu, 1997

	Mother's touch vs rectal thermometry	LR+: 1.20 ** LR-: 0.14 ** Sensitivity: 0.97, 95% CI [0.95;0.99] * Specificity: 0.19, 95% CI [0.16;0.22] * TP: 399/1120 FP: 574/1120 TN: 136/1120 FN: 11/1120 *index test can be considered as clinically helpful for the presence of fever*	1, 1120 (diagnostic accuracy study)	
	Doctor's touch vs rectal thermometry	LR+: 1.23 ** LR-: 0.62 ** Sensitivity: 0.93, 95% CI [0.89;0.96] Specificity: 0.24, 95% CI [0.18;0.29] TP: 104/182 FP: 53/182 TN: 17/182 FN: 8/182 *index test can be considered as not clinically helpful for the presence of fever*	1, 182 (diagnostic accuracy study)	Akinbami, 2010
	Nurse's touch vs rectal thermometry	LR+: 1.23 ** LR-: 0.62 ** Sensitivity: 0.94, 95% CI [0.90;0.97] Specificity: 0.26, 95% CI [0.19;0.31] TP: 105/182 FP: 52/182 TN: 18/182 FN: 7/182 *index test can be considered as not clinically helpful for the presence of fever*		
Fever (rectal temperature ≥ 38.1 °C)	Doctor's touch vs rectal thermometry	LR+: 2.53 ** LR-: 0.40 ** Sensitivity: 0.71, 95% CI [0.61;0.80] * Specificity: 0.72, 95% CI [0.62;0.80] * TP: 70/201 *** FP: 29/201 *** TN: 74/201 *** FN: 28/201 *** *index test can be considered as clinically helpful for the presence of fever*	1, 201 (diagnostic accuracy study, case control design)	Hung, 2000
Palpation vs axillary thermometry				
Fever (axillary temperature ≥ 38 °C)	Mother's touch vs axillary thermometry	LR+: 8.07 ** LR-: 0.27 ** Sensitivity: 0.76, 95% CI [0.68;0.83]	1, 169 (diagnostic accuracy study)	Alves, 2002

		Specificity: 0.91, 95% CI [0.74;0.98] TP: 104/169 FP: 3/169 *** TN: 29/169 FN: 33/169 *** *index test can be considered as clinically helpful for the presence of fever*		
		LR+: 1.79 ** LR-: 0.47 ** Sensitivity: 0.82, 95% CI [0.75;0.88] * Specificity: 0.54, 95% CI [0.46;0.62] * TP: 116/300 FP: 73/300 TN: 86/300 FN: 25/300 *index test can be considered as not clinically helpful for the presence of fever*	1, 300 (diagnostic accuracy study)	Asekun-Olarinmoye, 2009
Fever (axillary temperature ≥ 37.8 °C)		LR+: 1.66 ** LR-: 0.15 ** Sensitivity: 0.94, 95% CI [0.90;0.96] * Specificity: 0.44, 95% CI [0.40;0.48] * TP: 221/862 FP: 353/862 TN: 273/862 FN: 15/862 *index test can be considered as clinically helpful for the presence of fever*	1, 862 (diagnostic accuracy study)	Whybrew, 1998
	Medical staff's touch vs axillary thermometry	LR+: 2.84 ** LR-: 0.09 ** Sensitivity: 0.94, 95% CI [0.90;0.96] * Specificity: 0.67, 95% CI [0.64;0.70] * TP: 257/1086 FP: 268/1086 TN: 544/1086 FN: 17/1086 *index test can be considered as clinically helpful for the presence of fever*	1, 1086 (diagnostic accuracy study)	
Fever (axillary temperature ≥ 37.5 °C)		LR+: 3.64 ** LR-: 0.64 ** Sensitivity: 0.44, 95% CI [0.33;0.56] **** Specificity: 0.88, 95% CI [0.81;0.93] **** TP: 34/217 FP: 17/217 TN: 123/217 FN: 43/217	1, 217 (diagnostic accuracy study)	Clough, 2007

		index test can be considered as clinically helpful for the presence of fever		
	Mother's touch vs axillary thermometry	LR+: 1.30 ** LR-: 0.49 ** Sensitivity: 0.82 ££ Specificity: 0.37 ££ TP: £ FP: £ TN: £ FN: £ *index test can be considered as not clinically helpful for the presence of fever*	1, 113 (diagnostic accuracy study)	Odinaka, 2014
		LR+: 2.30 ** LR-: 0.18 ** Sensitivity: 0.89, 95%CI [0.83;0.94] **** Specificity: 0.61, 95%CI [0.54;0.68] **** TP: 125/359 FP: 85/359 TN: 134/359 FN: 15/359 *index test can be considered as clinically helpful for the presence of fever*	1, 359 (diagnostic accuracy study)	Okposio, 2012
	Attendant's touch vs axillary thermometry	LR+: 2.03 LR-: 0.24 Sensitivity: 0.86, 95% CI [0.81;0.91] Specificity: 0.57, 95% CI [0.51;0.63] TP: 178/463 FP: 109/463 TN: 147/463 FN: 28/463 *index test can be considered as clinically helpful for the presence of fever*	1, 463 (diagnostic accuracy study)	Singh, 2003
	Attendant's touch on the forehead vs axillary thermometry	LR+: 1.43 LR-: 0.43 Sensitivity: 0.81, 95% CI [0.69;0.90] Specificity: 0.43, 95% CI [0.31;0.55] TP: £ FP: £ TN: £ FN: £	1, ? (diagnostic accuracy study)	

		index test can be considered as not clinically helpful for the presence of fever		
	Doctor's touch vs axillary thermometry	LR+: 3.08 LR-: 0.20 Sensitivity: 0.85, 95% CI [0.80;0.90] Specificity: 0.72, 95% CI [0.67;0.77] TP: 176/463 FP: 72/463 TN: 185/463 FN: 30/463 *index test can be considered as clinically helpful for the presence of fever*	1, 463 (diagnostic accuracy study)	
Fever (axillary temperature ≥ 37.2 °C)	Mother's touch on the forehead vs axillary thermometry	LR+: 1.69 ** LR-: 0.65 ** Sensitivity: 0.96, 95% CI [0.90;0.99] * Specificity: 0.43, 95% CI [0.28;0.59] * TP: 79/126 *** FP: 25/126 *** TN: 19/126 *** FN: 3/126 *** *index test can be considered as not clinically helpful for the presence of fever*	1, 126 (diagnostic accuracy study)	Wammanda, 2009
Palpation vs oral or rectal thermometry				
Fever (oral or rectal temperature ≥ 38 °C)	Nurse's touch vs oral or rectal thermometry	LR+: 32.56 ** LR-: 0.43 ** Sensitivity: 0.58, 95% CI [0.58;0.68] **** Specificity: 0.98, 95% CI [0.49;0.66] **** TP: 80/1149 FP: 18/1149 TN: 993/1149 FN: 58/149 *index test can be considered as clinically helpful for the presence of fever*	1, 1149 (diagnostic accuracy study)	Bergeson, 1974
Palpation vs oral thermometry				
Fever (oral temperature ≥37.5 °C)	Caregiver's touch vs oral thermometry	LR+: 1.16 ** LR-: 0.78 ** Sensitivity: 0.67, 95% CI [0.50;0.81] * Specificity: 0.43, 95% CI [0.30;0.56] * TP: 26/100 FP: 35/100 TN: 26/100 FN: 13/100 *index test can be considered as not clinically helpful for the presence of fever*	1, 100 (diagnostic accuracy study)	Chaturvedi, 2003

	Medical staff's touch vs oral thermometry	LR+: 2.20 ** LR-: 0.32 ** Sensitivity: 0.79, 95% CI [0.64;0.91] * Specificity: 0.64, 95% CI [0.51;0.76] * TP: 31/100 FP: 22/100 TN: 39/100 FN: 8/100 *index test can be considered as clinically helpful for the presence of fever*		
Palpation vs oral or axillary thermometry				
Fever (oral or axillary temperature >37.4 °C)	Mother's touch vs oral or axillary thermometry	LR+: 7.80 ** LR-: 0.13 ** Sensitivity: 0.89, 95% CI [0.82;0.94] * Specificity: 0.89, 95% CI [0.83;0.93] * TP: 104/301 FP: 21/301 *** TN: 163/301 FN: 13/301 *** *index test can be considered as clinically helpful for the presence of fever*	1, 301 (diagnostic accuracy study)	Singhi, 1990
	Mother's touch on the forehead vs oral or axillary thermometry	LR+: 7.86** LR-: 0.19 ** Sensitivity: 0.83, 95% CI [0.69;0.93] * Specificity: 0.89, 95% CI [0.77;0.96] * TP: 35/89 FP: 5/89 *** TN: 42/89 *** FN: 7/89 *index test can be considered as clinically helpful for the presence of fever*	1, 89 (diagnostic accuracy study)	

* 95% CI calculated using Review Manager software
** LR calculated using Review Manager software
*** TP/FP/TN/FN calculated using Review Manager software
**** sensitivity/specificity calculated using Review Manager software
£ No raw data available
££ 95%CI cannot be calculated

Author, Year	Could the selection of patients have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?	Could the reference standard, its conduct, or its interpretation have introduced bias?	Could the patient flow have introduced bias?	Other limitations
Abdulkadir, 2014	Yes, patients that were prior to presentation measured with a thermometer were not excluded	Yes, site of palpation was not fixed	No	No, all patients presenting in a time frame of 4 months were included	No
Akinbami, 2010	Unclear, no information about prior temperature measurements or antipyretic use	Yes, site of palpation was not fixed	No	No, all patients presenting in a time frame of 4 months were included if consented by caregivers	Yes, not reported how many doctors and nurses participated
Alves, 2002	Yes, patients that were prior to presentation measured with a thermometer were not excluded	Yes, site of palpation was the neck	Yes, axillary temperatures measured, while rectal temperature measurements are considered as the gold standard in children	No, all patients presenting in a time frame of 2 months were included	No
Asekun-Olarinmoye, 2009	Unclear, no information about prior temperature measurements or antipyretic use	Yes, site of palpation was not fixed	Yes, axillary temperatures measured, while rectal temperature measurements are considered as the gold standard in children	No, all patients presenting in 4 randomly selected health care centres were included	No
Bergeson, 1974	No	Yes, site of palpation was not fixed	Yes, same cut-off value was used to determine fever (≥ 38 °C) for oral and rectal temperature measurements	No, all patients presenting in a time frame of 2 months were included	Yes, only 3 nurses assessed temperatures
Callanan, 2003	Yes, patients that were prior to presentation measured with a thermometer were not excluded	Yes, site of palpation was not fixed	No	No, all patients presenting in a time frame of 3 months were included	No
Chaturverdi, 2003	No, patients that had previously temperature measured by thermometer	Yes, site of palpation was not fixed	No	No	Yes, not reported how many doctors and nurses participated

	or received antipyretics were excluded				
Clough, 2007	No, patients of which prior information was received were excluded	Unclear, site of palpation was not defined	No	No	No
Hooker, 1996	Yes, patients that were prior to presentation measured with a thermometer or received antipyretics were not excluded	Yes, site of palpation was not fixed	No	Yes, patients were only included when one of the investigators was able to be present	No
Hung, 2000	Yes, participants were selected using a case-control design, which can lead to confounding	Yes, site of palpation was not fixed	No	Unclear, not stated how many observations a single clinician made and how many times a single patient was examined	No
Katz-Sidlow, 2009	Yes, patients receiving antipyretics were not excluded	Yes, site of palpation was not fixed	No	No	Yes, not clear how many patients had temperature measured at home and thus were excluded in the second analysis
Nwanyanwu, 1997	Unclear, no information about prior temperature measurements or antipyretic use	No	No	No	Yes, not reported how many clinical officers participated
Odinaka, 2014	Unclear, no information about prior temperature measurements or antipyretic use	Yes, site of palpation was not fixed	Yes, axillary temperatures measured, while rectal temperature measurements are considered as the gold standard in children	No	No
Okposio, 2012	No, patients that had previously temperature measured by thermometer or received antipyretics were excluded	Yes, site of palpation was not fixed	Yes, axillary temperatures measured, while rectal temperature measurements are considered as the gold standard in children	No	No

Singh, 2003	Unclear, no information about prior temperature measurements or antipyretic use	Yes, site of palpation was not fixed	No	No	Yes, not reported how many patients were included in the analysis of determining fever by palpating the forehead
Singhi, 1990	No, the prior assessment of the temperature with a thermometer was analysed and found not to be of influence on the subjective assessment of fever	Yes, site of palpation was not fixed	Yes, axillary and oral temperatures measured, while rectal temperature measurements are considered as the gold standard in children	Yes, only patients presenting before noon were included	No
Wammanda, 2009	Unclear, no information about prior temperature measurements or antipyretic use	No	Yes, axillary temperatures measured, while rectal temperature measurements are considered as the gold standard in children	Yes, only patients presenting during shifts of the author were included	No
Whybrew, 1998	Unclear, no information about prior temperature measurements or antipyretic use	Yes, multiple sites of palpation	Yes, axillary temperatures measured, while rectal temperature measurements are considered as the gold standard in children	No	Yes, only 2 medical students assessed temperatures

Quality of evidence

	High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	0	
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Moderate [B]**	

Conclusion	Palpation vs rectal thermometry: There is evidence from 8 diagnostic accuracy studies concerning palpation: There is limited evidence from 5 diagnostic accuracy studies that palpation might be helpful for the diagnosis of fever, compared to rectal thermometry (Callanan 2003, Hooker 1996, Katz-Sidlow 2009, Nwanyanwu 1997, Hung 2000). In contrast, there is limited evidence from 3 diagnostic accuracy studies that palpation might not be helpful for the diagnosis of fever, compared to rectal thermometry (Abdulkadir 2014, Akinbami 2010, Chaturvedi 2003). Evidence is of moderate quality. Palpation vs axillary thermometry:

	There is evidence from 8 diagnostic accuracy studies concerning palpation: There is limited evidence from 5 diagnostic accuracy studies that palpation might be helpful for the diagnosis of fever, compared to axillary thermometry (Alves 2002, Clough 2007, Okposio 2012, Singh 2003, Whybrew 1998). In contrast, there is limited evidence from 3 diagnostic accuracy studies that palpation might not be helpful for the diagnosis of fever, compared to axillary thermometry (Asekun-Olarinmoye 2009, Odinaka 2014, Wammada 2009). Evidence is of moderate quality. Palpation vs oral thermometry: There is limited evidence from 1 diagnostic accuracy study that palpation might not be helpful for the diagnosis of fever, compared to oral thermometry (Chaturvedi 2003). Evidence is of moderate quality. Palpation vs oral/rectal thermometry: There is limited evidence from 1 diagnostic accuracy study that palpation might be helpful for the diagnosis of fever, compared to oral or rectal thermometry (Bergeson 1974). Evidence is of moderate quality. Palpation vs oral/axillary thermometry: There is limited evidence from 1 diagnostic accuracy study that palpation might be helpful for the diagnosis of fever, compared to oral or axillary thermometry (Singhi 1990). Evidence is of moderate quality.
Reference(s)	**Articles** Abdulkadir MB, Johnson WB, Ibraheem RM. *Validity and accuracy of maternal tactile assessment for fever in under-five children in north central Nigeria: a cross-sectional study*. BMJ Open. 2014, 4(10):e005776. Akinbami FO, Orimadegun AE, Tongo OO, Okafor OO, Akinyinka OO. *Detection of fever in children emergency care: comparisons of tactile and rectal temperatures in Nigerian children. BMC Res Notes*. 2010,3:108. Alves JG, Correia Jde B. *Ability of mothers to assess the presence of fever in their children without using a thermometer.* Trop Doct. 2002, 32(3):145-6. Asekun-Olarinmoye EO, Egbewale BE, Olajide FO. *Subjective assessment of childhood fever by mothers utilizing primary health care facilities in Osogbo, Osun State, Nigeria.* Niger J Clin Pract. 2009,12(4):434-8. Bergeson PS, Stienfeld HJ. *How dependable is palpation as a screening method for fever? Can touch substitute for thermometer readings?* Clin Pediatr (Phila). 1974, 13(4):350-1. Callanan D. *Detecting fever in young infants: reliability of perceived, pacifier, and temporal artery temperatures in infants younger than 3 months of age. Pediatr Emerg Care.* 2003, 19(4):240-3. Chaturvedi D, Vilhekar KY, Chaturvedi P, Bharambe MS. *Reliability of perception of fever by touch.* Indian J Pediatr. 2003, 70(11):871-3. Clough A. *Palpation for fever.* S Afr Med J. 2007, 97(9):829-30. Hooker EA, Smith SW, Miles T, King L. *Subjective assessment of fever by parents: comparison with measurement by noncontact tympanic thermometer and calibrated rectal glass mercury thermometer.* Ann Emerg Med. 1996, 28(3):313-7. Hung OL, Kwon NS, Cole AE, Dacpano GR, Wu T, Chiang WK, Goldfrank LR. *Evaluation of the physician's ability to recognize the presence or absence of anemia, fever, and jaundice*. Acad Emerg Med. 2000, 7(2):146-56. Katz-Sidlow RJ, Rowberry JP, Ho M. *Fever determination in young infants: prevalence and accuracy of parental palpation.* Pediatr Emerg Care. 2009, 25(1):12-4. Nwanyanwu OC, Ziba C, Redd SC, Luby SP. *Palpation as a method of fever determination in Malawian children who are less than 5 years old: how reliable is it?* Ann Trop Med Parasitol. 1997, 91(4):359-63.

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Fever – Measuring axillary temperature (Diagnostics)

Question (PICO)	In people (P), should axillary temperature (I) be used to diagnose fever (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh thermometers] or thermometer*:ti,ab,kw 2. [mh fever] OR pyrexia:ti,ab,kw OR hyperthermia:ti,ab,kw OR fever*:ti,ab,kw 3. [mh Sensitivity and specificity] OR Sensitivity:ti,ab,kw OR Specificity:ti,ab,kw OR "Pre-test probability":ti,ab,kw OR "Pretest probability":ti,ab,kw OR "Post-test probability":ti,ab,kw OR "Posttest probability":ti,ab,kw OR "Predictive value":ti,ab,kw OR "Predictive values":ti,ab,kw OR "Likelihood ratio":ti,ab,kw OR "Likelihood ratios":ti,ab,kw 4. 1-3 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Thermometers[Mesh] OR thermometer*[TIAB] 2. Fever[Mesh] OR fever*[TIAB] OR pyrexia[TIAB] OR hyperthermia*[TIAB] 3. "Sensitivity and specificity"[Mesh] OR "Sensitivity"[TIAB] OR "Specificity"[TIAB] OR "Pre-test probability"[TIAB] OR "Pretest probability"[TIAB] OR "Post-test probability"[TIAB] OR "Posttest probability"[TIAB] OR "Predictive value"[TIAB] OR "Predictive values"[TIAB] OR "Likelihood ratio"[TIAB] OR "Likelihood ratios"[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Thermometer/exp OR thermometer*:ab,ti 2. Fever/exp OR fever*:ab,ti OR pyrexia:ab,ti OR hyperthermia/exp OR hyperthermia:ab,ti 3. 'Diagnostic accuracy'/exp OR 'Sensitivity and specificity'/exp OR 'Sensitivity':ab,ti OR 'Specificity':ab,ti OR ((Pre-test or pretest) near/5 probability):ab,ti OR 'Post-test probability':ab,ti OR 'Posttest probability':ab,ti OR 'Predictive value':ab,ti OR 'Predictive values':ab,ti OR 'Likelihood ratio':ab,ti OR 'Likelihood ratios':ab,ti 4. 1-3 AND

	Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	14 October 2015
In/Exclusion criteria	**Population:** children or adults (with or without fever) **Intervention:** measurement of axillary temperature with a digital thermometer **Comparison:** measurement of rectal temperature with any type of thermometer **Outcome:** Diagnosis of fever (true positives, false positives, true negatives, false negatives), Level of agreement between two methods (i.e. level of agreement) **Design**: Include: a systematic review: inclusion of diagnostic studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. If no systematic review of diagnostic studies is present, individual diagnostic studies (randomized controlled trial or diagnostic accuracy study) will be included. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Craig, 2000, United Kingdom	Diagnostics: Systematic review	40 studies including 5528 children and young people from birth to 18 years comparing temperature measured at the axilla (index test) with temperature measured at the rectum (reference standard) using the same type of measuring device at both sites in each patient	Index test: axillary temperature with an electronic thermometer Reference standard: rectal temperature with an electronic thermometer	
Hebbar, 2005, USA	Diagnostics: Diagnostic accuracy study	44 paediatric intensive care unit patients Median age 11.5 months (25th–75th percentile 2–34 months)	Index test: digital axillary thermometer (Allegiance Healthcare Corporation, McGaw Park, IL) Reference standard: digital rectal thermometer (Allegiance Healthcare Corporation, McGaw Park, IL)	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Mean difference in temperature (°C)	Axillary temperature (electronic thermometer) vs rectal temperature (electronic thermometer)	MD [95% limits of agreement]: 0.85 [-0.19;1.90] £†	9, 1685 vs 1685 (diagnostic accuracy studies)	Craig, 2000
	Axillary temperature (digital thermometer) vs rectal temperature (digital)	MD [95% limits of agreement]: -0.16 [-0.76;1.08] £†	1, 40 vs 40 (diagnostic accuracy studies) (power-analysis)	Hebbar, 2005

£ No raw data available

† Imprecision (lack of data)

Quality of evidence

Author, Year	Could the selection of patients have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?	Could the reference standard, its conduct, or its interpretation have introduced bias?	Could the patient flow have introduced bias?	Other limitations
Craig, 2000	Unclear	Yes	Yes	No	
Hebbar, 2005	No	Yes	Yes	No	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	0	
Inconsistency	0	
Indirectness	-1	No lay people (i.e. hospital setting)
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is limited evidence showing that the difference between temperature readings at the axilla and rectum using either mercury or electronic thermometers showed wide variation across studies (Craig 2000 and Hebbar 2005). Evidence is of low quality
Reference(s)	**Articles** Hebbar K, Fortenberry JD, Rogers K, Merritt R, Easley K. *Comparison of temporal artery thermometer to standard temperature measurements in pediatric intensive care unit patients*. Pediatr Crit Care Med 2005, 6(5):557-561. **Systematic reviews** Craig JV, Lancaster GA, Williamson PR, Smyth RL. *Temperature measured at the axilla compared with rectum in children and young people: systematic review*. BMJ 2000, 320(7243):1174-1178.

Fever – Measuring oral temperature (Diagnostics)

Question (PICO)	In people (P), should oral temperature (I) versus rectal temperature (C)) be used to diagnose fever (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh thermometers] or thermometer*:ti,ab,kw 2. [mh fever] OR pyrexia:ti,ab,kw OR hyperthermia:ti,ab,kw OR fever*:ti,ab,kw 3. [mh Sensitivity and specificity] OR Sensitivity:ti,ab,kw OR Specificity:ti,ab,kw OR "Pre-test probability":ti,ab,kw OR "Pretest probability":ti,ab,kw OR "Post-test probability":ti,ab,kw OR "Posttest probability":ti,ab,kw OR "Predictive value":ti,ab,kw OR "Predictive values":ti,ab,kw OR "Likelihood ratio":ti,ab,kw OR "Likelihood ratios":ti,ab,kw 4. 1-3 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Thermometers[Mesh] OR thermometer*[TIAB] 2. Fever[Mesh] OR fever*[TIAB] OR pyrexia[TIAB] OR hyperthermia*[TIAB]

	3. "Sensitivity and specificity"[Mesh] OR "Sensitivity"[TIAB] OR "Specificity"[TIAB] OR "Pre-test probability"[TIAB] OR "Pretest probability"[TIAB] OR "Post-test probability"[TIAB] OR "Posttest probability"[TIAB] OR "Predictive value"[TIAB] OR "Predictive values"[TIAB] OR "Likelihood ratio"[TIAB] OR "Likelihood ratios"[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Thermometer/exp OR thermometer*:ab,ti 2. Fever/exp OR fever*:ab,ti OR pyrexia:ab,ti OR hyperthermia/exp OR hyperthermia:ab,ti 3. 'Diagnostic accuracy'/exp OR 'Sensitivity and specificity'/exp OR 'Sensitivity':ab,ti OR 'Specificity':ab,ti OR ((Pre-test or pretest) near/5 probability):ab,ti OR 'Post-test probability':ab,ti OR 'Posttest probability':ab,ti OR 'Predictive value':ab,ti OR 'Predictive values':ab,ti OR 'Likelihood ratio':ab,ti OR 'Likelihood ratios':ab,ti 4. 1-3 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	14 October 2015
In/Exclusion criteria	**Population:** children or adults (with or without fever) **Intervention:** measurement of oral temperature with a digital thermometer **Comparison:** measurement of rectal temperature with any type of thermometer **Outcome:** Diagnosis of fever (true positives, false positives, true negatives, false negatives), Level of agreement between two methods (i.e. level of agreement) **Design**: Include: a systematic review: inclusion of diagnostic studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. If no systematic review of diagnostic studies is present, individual diagnostic studies (randomized controlled trial or diagnostic accuracy study) will be included. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Jensen, 1994, Denmark	Diagnostics: Diagnostic accuracy study	184 patients (72 women, 112 men), median age 70 years (18-95 years) at the Department of Urology and Endocrinology (study 1, CRAFTEMP thermometer) 91 patients (41 women, 50 men), median age 59 years (18-96 years) at the Department Gastroenterological Surgery (study 2, TERUMO WCT)	Index test 1: electronic oral thermometer (CRAFTEMP) Index test 2: electronic oral thermometer (TERUMO WCT) Reference standard: rectal glass mercury thermometer	Fever is defined as oral measurements ≥ 37.0°C or rectal measurements ≥ 37.5°C

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Diagnosis of fever	Electronic oral thermometry (CRAFTEMP) vs rectal glass mercury thermometry	Sensitivity: 0.44, 95%CI [0.14;0.79] Specificity: 0.93, 95%CI [0.88;0.96] Prevalence:0.05 (Nassisi 2012) TP: 4/184 (2%)* FP: 12/184 (6%)* TN: 163/184 (89%)* FN: 5/184 (3%)*	1, 184 vs 184 (Diagnostic accuracy study)	Jensen 1994
	Electronic oral thermometry (TERUMO WCT) vs rectal glass mercury thermometry	Sensitivity: 0.60, 95%CI [0.15;0.95] Specificity: 0.93, 95% CI [0.85;0.97] Prevalence:0.05 (Nassisi 2012) TP: 3/91 (3%)* FP: 6/91 (7%)* TN: 80/91 (88%)* FN: 2/91 (2%)*	1, 91 vs 91 (diagnostic accuracy study)	

* Calculations done by the reviewer(s) using Review Manager software
TP: true positives, FP: false positives, TN: true negatives, FN: false negatives.

Quality of evidence

Author, Year	Could the selection of patients have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?	Could the reference standard, its conduct, or its interpretation have introduced bias?	Could the patient flow have introduced bias?	Other limitations
Jensen, 1994	Unclear	Yes	Yes	No	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	0	
Inconsistency	0	
Indirectness	-1	No lay people (i.e. hospital setting)
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is limited evidence showing that rectal (mercury glass) thermometry must be preferred to oral digital thermometry for daily routine measurements (Jensen 1994). Evidence is of low quality.
Reference(s)	**Articles** Jensen BN, Jeppesen LJ, Mortensen BB, Kjaergaard B, Andreasen H, Glavind K. *The superiority of rectal thermometry to oral thermometry with regard to accuracy*. J Adv Nurs 1994, 20(4):660-665. Nassisi D, Oishi ML. *Evidence-based guidelines for evaluation and antimicrobial therapy for common emergency department infections*. Emerg Med Pract 2012, 14(1):1-28; quiz 28-29.

Fever – Measuring temporal artery temperature (Diagnostics)

Question (PICO)	In people (P), should temporal artery temperature (I) be used to diagnose fever (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh thermometers] or thermometer*:ti,ab,kw 2. [mh fever] OR pyrexia:ti,ab,kw OR hyperthermia:ti,ab,kw OR fever*:ti,ab,kw 3. [mh Sensitivity and specificity] OR Sensitivity:ti,ab,kw OR Specificity:ti,ab,kw OR "Pre-test probability":ti,ab,kw OR "Pretest probability":ti,ab,kw OR "Post-test probability":ti,ab,kw OR "Posttest probability":ti,ab,kw OR "Predictive value":ti,ab,kw OR "Predictive values":ti,ab,kw OR "Likelihood ratio":ti,ab,kw OR "Likelihood ratios":ti,ab,kw 4. 1-3 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Thermometers[Mesh] OR thermometer*[TIAB] 2. Fever[Mesh] OR fever*[TIAB] OR pyrexia[TIAB] OR hyperthermia*[TIAB] 3. "Sensitivity and specificity"[Mesh] OR "Sensitivity"[TIAB] OR "Specificity"[TIAB] OR "Pre-test probability"[TIAB] OR "Pretest probability"[TIAB] OR "Post-test probability"[TIAB] OR "Posttest probability"[TIAB] OR "Predictive value"[TIAB] OR "Predictive values"[TIAB] OR "Likelihood ratio"[TIAB] OR "Likelihood ratios"[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Thermometer/exp OR thermometer*:ab,ti 2. Fever/exp OR fever*:ab,ti OR pyrexia:ab,ti OR hyperthermia/exp OR hyperthermia:ab,ti 3. 'Diagnostic accuracy'/exp OR 'Sensitivity and specificity'/exp OR 'Sensitivity':ab,ti OR 'Specificity':ab,ti OR ((Pre-test or pretest) near/5 probability):ab,ti OR 'Post-test probability':ab,ti OR 'Posttest probability':ab,ti OR 'Predictive value':ab,ti OR 'Predictive values':ab,ti OR 'Likelihood ratio':ab,ti OR 'Likelihood ratios':ab,ti 4. 1-3 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	14 October 2015
In/Exclusion criteria	**Population:** children or adults (with or without fever) **Intervention:** measurement of infrared temporal artery temperature **Comparison:** measurement of rectal temperature with any type of thermometer **Outcome:** Diagnosis of fever (true positives, false positives, true negatives, false negatives), Level of agreement between two methods (i.e. level of agreement) **Design**: Include: a systematic review: inclusion of diagnostic studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. If no systematic review of diagnostic studies is present, individual diagnostic studies (randomized controlled trial or diagnostic accuracy study) will be included. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks

Hebbar, 2005, USA	Diagnostics: Diagnostic accuracy study	44 pediatric intensive care unit patients Median age 11.5 months (25th–75th percentile 2–34 months)	Index test: temporal artery infrared thermometer (Temporal Scanner; Exergen Corporation, Watertown, MA) Reference standard: digital rectal thermometer (Allegiance Healthcare Corporation, McGaw Park, IL)	Temperature measurements were taken by placing the instrument probe on the patient's forehead and then sweeping it laterally to the temporal area until the hairline of the temporal scalp was reached
Siberry, 2002, USA	Diagnostics: Diagnostic accuracy study	275 subjects up to 2 years old (The average age was 11.2 months, ranging from 0 to 24 months) presenting for an acute care visit to 2 primary care pediatric sites were recruited. Patients more likely to have fever were preferentially recruited.	Index test: Temporal artery thermometer: Home model (Infrared Temporal Scanner ST-Pt, Exergen Corp.) Reference standard: digital rectal thermometer (Sure-Temp, Welch Allyn)	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Temperature (°C)	Temporal artery temperature (infrared thermometer) vs rectal temperature (digital)	MD [95% limits of agreement]: -0.04 [-1.81;1.88]	1, 40 vs 40 (diagnostic accuracy studies)	Hebbar, 2005
Fever (defined as temperature 38.5°C)		Sensitivity:0.93, 95%CI [0.66;1.00] Specificity:0.46, 95%CI [0.40;0.52] Prevalence:0.05 (Nassisi 2012) TP: 13/275(5%)* FP: 141/275 (51%)* TN: 120/275 (44%)* FN: 1/275 (1%)*	1, 275 vs 275 (diagnostic accuracy studies)	Siberry, 2002
Fever (defined as temperature 38.5°C)		Sensitivity:1.00, 95%CI [0.75;1.00] Specificity:0.84, 95%CI [0.79;0.88] Prevalence:0.05 (Nassisi 2012) TP: 13/275(5%)* FP: 42/275 (15%)* TN: 219/275 (80%)* FN: 0/275 (0%)*		

* Calculations done by the reviewer(s) using Review Manager software
TP: true positives, FP: false positives, TN: true negatives, FN: false negatives.

Quality of evidence

Author, Year	Could the selection of patients have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?	Could the reference standard, its conduct, or its interpretation have introduced bias?	Could the patient flow have introduced bias?	Other limitations
Hebbar, 2005	No	Yes	Yes	No	
Siberry, 2002	No	Unclear	Unclear	No	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	0	
Inconsistency	0	
Indirectness	-1	No lay people (i.e. hospital setting)
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is limited evidence showing that temporal temperatures (forehead) measured with an infrared thermometer do not reliably predict rectal temperatures (measured by digital thermometry). (Hebbar 2005 and Siberry 2002). Evidence is of low quality.
Reference(s)	**Articles** Hebbar K, Fortenberry JD, Rogers K, Merritt R, Easley K. *Comparison of temporal artery thermometer to standard temperature measurements in pediatric intensive care unit patients*. Pediatr Crit Care Med 2005, 6(5):557-561. Nassisi D, Oishi ML. *Evidence-based guidelines for evaluation and antimicrobial therapy for common emergency department infections*. Emerg Med Pract 2012, 14(1):1-28; quiz 28-29. Siberry GK, Diener-West M, Schappell E, Karron RA. *Comparison of temple temperatures with rectal temperatures in children under two years of age*. Clin Pediatr (Phila) 2002, 41(6):405-414.

Fever – Measuring tympanic membrane temperature (Diagnostics)

Question (PICO)	In people (P), should tympanic membrane temperature (I) be used to diagnose fever (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh thermometers] or thermometer*:ti,ab,kw 2. [mh fever] OR pyrexia:ti,ab,kw OR hyperthermia:ti,ab,kw OR fever*:ti,ab,kw 3. [mh Sensitivity and specificity] OR Sensitivity:ti,ab,kw OR Specificity:ti,ab,kw OR "Pre-test probability":ti,ab,kw OR "Pretest probability":ti,ab,kw OR "Post-test probability":ti,ab,kw OR "Posttest probability":ti,ab,kw OR "Predictive value":ti,ab,kw OR "Predictive values":ti,ab,kw OR "Likelihood ratio":ti,ab,kw OR "Likelihood ratios":ti,ab,kw 4. 1-3 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Thermometers[Mesh] OR thermometer*[TIAB] 2. Fever[Mesh] OR fever*[TIAB] OR pyrexia[TIAB] OR hyperthermia*[TIAB]

	3. "Sensitivity and specificity"[Mesh] OR "Sensitivity"[TIAB] OR "Specificity"[TIAB] OR "Pre-test probability"[TIAB] OR "Pretest probability"[TIAB] OR "Post-test probability"[TIAB] OR "Posttest probability"[TIAB] OR "Predictive value"[TIAB] OR "Predictive values"[TIAB] OR "Likelihood ratio"[TIAB] OR "Likelihood ratios"[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Thermometer/exp OR thermometer*:ab,ti 2. Fever/exp OR fever*:ab,ti OR pyrexia:ab,ti OR hyperthermia/exp OR hyperthermia:ab,ti 3. 'Diagnostic accuracy'/exp OR 'Sensitivity and specificity'/exp OR 'Sensitivity':ab,ti OR 'Specificity':ab,ti OR ((Pre-test or pretest) near/5 probability):ab,ti OR 'Post-test probability':ab,ti OR 'Posttest probability':ab,ti OR 'Predictive value':ab,ti OR 'Predictive values':ab,ti OR 'Likelihood ratio':ab,ti OR 'Likelihood ratios':ab,ti 4. 1-3 AND
Search date	14 October 2015
In/Exclusion criteria	**Population:** children or adults (with or without fever) **Intervention:** measurement of tympanic membrane temperature by infrared thermometers **Comparison:** measurement of rectal temperature with any type of thermometer **Outcome:** Diagnosis of fever (true positives, false positives, true negatives, false negatives), Level of agreement between two methods (i.e. level of agreement) **Design**: Include: a systematic review: inclusion of diagnostic studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. If no systematic review of diagnostic studies is present, individual diagnostic studies (randomized controlled trial or diagnostic accuracy study) will be included. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Zhen, 2015, China	Diagnostics: Systematic review	25 diagnostic accuracy studies performed in children (<18 years) assessing the accuracy of infrared tympanic thermometry in the diagnosis of paediatric fever	Index test: infrared tympanic membrane thermometry Reference standard: rectal thermometry (electronic or mercury)	Fever was defined as temperature ≥ 38.0°C. If the articles included several different cut-offs, we selected the cut-off that is closest to 38.0°C and dropped the others.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Temperature (°C)	Infrared tympanic thermometry vs rectal thermometry	Pooled sensitivity: 0.70, 95% CI [0.63;0.76] pooled specificity: 0.86, 95%CI [0.85;0.87], prevalence fever (Nassisi 2012): 0.05 TP: 151/4320(3%)* FP: 575/4320 (13%)* TN: 3529/4320 (82%)* FN: 65/4320 (2%)*	1, 4320 vs 4320 (diagnostic accuracy studies)	Zhen 2015

* Calculations done by the reviewer(s) using Review Manager software
TP: true positives, FP: false positives, TN: true negatives, FN: false negatives.

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See Zhen 2015 (QUADAS score 12±1)
Imprecision	0	
Inconsistency	0	
Indirectness	-1	No lay people (i.e. hospital settings)
Publication bias	-1	See Zhen 2015
QUALITY (GRADE)	**Final grading Very low [C]**	

Conclusion	There is limited evidence from 1 systematic review showing that the accuracy of infrared tympanic thermometry is high (Zhen 2015). Evidence is of low quality.
Reference(s)	**Articles** Nassisi D, Oishi ML. *Evidence-based guidelines for evaluation and antimicrobial therapy for common emergency department infections*. Emerg Med Pract 2012, 14(1):1-28; quiz 28-29. **Systematic reviews** Zhen C, Xia Z, Ya Jun Z, Long L, Jian S, Gui Ju C, Long L. *Accuracy of infrared tympanic thermometry used in the diagnosis of Fever in children: a systematic review and meta-analysis*. Clin Pediatr (Phila). 2015, 54(2):114-126

Fever – Drinking water (First aid)

Question (PICO)	In children (P), is drinking water (I) compared to not drinking water (C) effective as a first aid treatment for fever (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh fever] OR pyrexia:ti,ab,kw OR hyperthermia:ti,ab,kw OR fever*:ti,ab,kw 2. [mh drinking] OR drink*:ti,ab,kw OR [mh "drinking water"] 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "fever"[Mesh] OR fever*[TIAB] OR "pyrexia"[TIAB] OR hyperthermia*[TIAB] 2. Drinking[Mesh] OR ((fluid[TIAB] OR liquid[TIAB]) AND (consumption[TIAB] OR ingestion[TIAB])) OR drink*[TIAB] OR "drinking water"[Mesh] 3. "First Aid"[Mesh] OR "Community Health Workers"[Mesh] OR "Emergency Treatment"[Mesh:NoExp] OR "Emergency Medical Services"[Mesh:NoExp] OR "Emergency Service, Hospital"[Mesh] OR "Poison Control Centers"[Mesh] OR "Transportation of Patients"[Mesh] OR "Primary Health Care"[Mesh:NoExp] OR "Acute disease"[Mesh] OR "emergencies" [Mesh] OR "self care"[Mesh] OR "acute management" [TIAB] OR "immediate care" [TIAB] OR "prehospital treatment" [TIAB] OR "first aid"[TIAB] OR "self care"[TIAB] OR emergenc*[TIAB] OR treat*[TIAB] OR improv*[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Fever/exp OR fever*:ab,ti OR pyrexia:ab,ti OR hyperthermia/exp OR hyperthermia:ab,ti

	2. 'drinking'/exp OR ((fluid:ab,ti OR liquid:ab,ti) AND (consumption:ab,ti OR ingestion:ab,ti)) OR drink*:ab,ti OR 'drinking water'/exp 3. 'first aid'/exp OR 'health auxiliary'/exp OR 'emergency treatment'/de OR 'emergency health service'/exp OR 'poison center'/exp OR 'patient transport'/exp OR 'primary health care'/exp OR 'acute disease'/exp OR 'emergency'/exp OR 'self care'/exp OR 'acute management':ab,ti OR 'immediate care':ab,ti OR 'prehospital treatment':ab,ti OR 'self care':ab,ti OR 'first aid':ab,ti OR emergenc*:ab,ti OR treat*:ab,ti OR improv*:ab,ti 4. 1-2 AND
Search date	19 May 2015
In/Exclusion criteria	**Population**: Include: sick or injured children with fever. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Fever – Paracetamol (First aid)

Question (PICO)	In children (P), is taking paracetamol (I) compared to placebo or physical interventions (C) effective as a first aid treatment for fever (O)
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh fever] OR pyrexia:ti,ab,kw OR hyperthermia:ti,ab,kw OR fever*:ti,ab,kw 2. [mh acetaminophen] OR acetaminophen:ti,ab,kw OR paracetamol:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for systematic reviews and meta-analyses using the following search strategy: 1. "fever"[Mesh] OR fever*[TIAB] OR "pyrexia"[TIAB] OR hyperthermia*[TIAB] 2. Acetaminophen[Mesh] OR Paracetamol[TIAB] OR acetaminophen[TIAB] 3. ((((((((((Meta-Analysis as Topic[Mesh])) OR ((meta analy*[TIAB]))) OR ((metaanaly*[TIAB]))) OR ((Meta-Analysis[Publication Type]))) OR ((systematic review*[TIAB] OR systematic overview*[TIAB]))) OR ((Review Literature as Topic[Mesh])))) OR ((cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB]))) OR ((reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB]))) OR ((((selection criteria[TIAB] OR data extraction[TIAB])) AND ((Review[PT]))))) NOT ((Comment[PT] OR Letter[PT] OR Editorial[PT] OR animal[Mesh] NOT (animal[Mesh] AND human[Mesh]))) 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Fever/exp OR fever*:ab,ti OR pyrexia:ab,ti OR hyperthermia/exp OR hyperthermia:ab,ti 2. Paracetamol/exp OR paracetamol:ab,ti OR acetaminophen:ab,ti 3. 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti 4. 1-3 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in MEDLINE (via PubMed interface).
Search date	19 May 2015
In/Exclusion criteria	**Population**: Include: sick or injured children with fever. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. Studies that compare paracetamol to another antipyretic drug without placebo group. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects).

	Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Meremikwu, 2002, Nigeria	Systematic review (Cochrane)	12 trials including 1509 children, aged between 3 months and 15 years, with fever	1. Paracetamol 2. Physical methods (sponging (with tepid or ice water or with alcohol+water), fanning, cool blankets, unwrapping) 3. Placebo	Most likely, new studies will not change the conclusions of this review. Therefore, the decision was made not to search for more recent studies (between 2002 and present)

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Without fever by 2nd hour	Paracetamol vs placebo	Statistically significant: 17/25 vs 0/15 RR: 21.54, 95%CI [1.39; 333.99] (p=0.03) *In favour of paracetamol*	1, 25 vs 15 §	Meremikwu, 2002
	Paracetamol vs physical cooling methods	Statistically significant: 55/65 vs 23/55 RR: 2.03, 95%CI [1.47; 2.80] (p=0.000017) *In favour of paracetamol*	2, 65 vs 55 §	
Adverse events	Paracetamol vs placebo	Not statistically significant: 9/130 vs 4/124 RR: 1.84, 95%CI [0.65; 5.18] (p=0.25) ¥	3, 130 vs 124 §	
	Paracetamol vs physical cooling methods	Not statistically significant: 2/65 vs 6/55 RR: 0.26, 95%CI [0.07; 1.01] (p=0.052)	2, 65 vs 55 §	
Without fever by 1st hour		Not statistically significant: 28/65 vs 18/55 RR: 1.49, 95%CI [0.98; 2.25] (p=0.061) ¥		

¥ Imprecision (large variability of results)
§ Imprecision (limited sample size or low number of events)

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	see systematic review Meremikwu 2002
Imprecision	-1	Limited sample sizes/large variability of results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Moderate [B]**	

Conclusion	There is limited evidence from 1 systematic review in favour of paracetamol. (In making this evidence conclusion, we place a higher value on the outcome 'relief of fever after 2 hours over other outcomes) It was shown that paracetamol resulted in a statistically significant increase of relief of fever at 2nd hour, compared to placebo or physical outcomes (Meremikwu 2002), but at the 1st hour this could not be demonstrated. A statistically significant difference of adverse events, using paracetamol compared to placebo or physical methods, could not be demonstrated (Meremikwu 2002). Evidence is of moderate quality and results cannot be considered precise due to limited sample size and/or large variability of results.
Reference(s)	**Articles** Meremikwu MM, Oyo-Ita A. *Paracetamol versus placebo or physical methods for treating fever in children*. Cochrane Database of Systematic Reviews 2002, Issue 2, Art. No.: CD003676

Fever – Physical methods (First aid)

Question (PICO)	In children (P), is the use of physical methods (sponging, fanning, bathing) (I) compared to no intervention or paracetamol (C) effective as a first aid treatment for fever (O)
Search Strategy	Databases A Cochrane review "Physical methods versus drug placebo or no treatment for managing fever in children" was identified. An update of the search was performed starting from the end date of the search in the Cochrane review (2005). **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh fever] OR pyrexia:ti,ab,kw OR fever*:ti,ab,kw 2. Spong*:ti,ab,kw OR [mh baths] OR bath*:ti,ab,kw OR fanning:ti,ab,kw OR "physical methods":ti,ab,kw OR cool*:ti,ab,kw 3. 1-2 AND [filter 2005-2015] **MEDLINE** (via PubMed interface) for systematic reviews and meta-analyses using the following search strategy: 1. "fever"[Mesh] OR fever*[TIAB] OR "pyrexia"[TIAB] 2. Sponging[TIAB] OR baths[Mesh] OR bath*[TIAB] OR fanning[TIAB] OR "physical methods"[TIAB] OR cool*[TIAB] 3. Child[Mesh] OR child*[TIAB] 4. 1-3 AND [filter 2005 – 2015] **Embase** (via Embase.com interface) using the following search strategy: 1. Fever/exp OR fever*:ab,ti OR pyrexia:ab,ti

	2. Sponging:ab,ti OR bath/exp OR bath*:ab,ti OR fanning:ab,ti OR 'physical methods':ab,ti OR cool*:ab,ti 3. Child/exp OR child*:ab,ti 4. 1-3 AND [filter 2005-2015] Guidelines, systematic reviews, retrieved with the above searches, and used as source for individual studies: Meremikwu, 2003 Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in MEDLINE (via PubMed interface).
Search date	29 May 2015
In/Exclusion criteria	**Population**: Include: sick or injured children with fever. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Studies on the use of fanning, bathing (in tepid/warm/ice water or in alcohol combined with water) or sponging (tepid/warm/ice water) as a treatment for fever. Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. Studies on the combination of physical methods and antipyretic drugs. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Aluka, 2013, Nigeria	Experimental: Randomized controlled trial	88 children (48 males, 40 females) between the age of 1 and 10 years, attending the Children Emergency Room and the Children Outpatient of the Universit of Calabar Teaching Hospital with fever,	1. Cold water sponging (n=44): subjects were completely undressed and sponged with cold water from head to toe. Sponging was done for a period of 30 minutes. 2. Paracetamol (n=44): 15 mg/kg	minimum sample size was calculated: approximately 40 subjects in each group + 10% attrition = 44 subjects in each group

		between October 2008 and January 2009.	All subjects were observed for a period of 120 minutes.	
Hunter, 1973, Australia	Experimental: Randomized controlled trial	67 children between 6 months and 5 years with temperature greater than 39.5°C	1. Placebo (n=6) 2. Aspirin alone 5-12 mg/kg(n=12) 3. Paracetamol alone 5-10 mg/kg (n=12) 4. Paracetamol 5-12 mg/kg plus sponging (n=13) 5. Tepid sponging alone (n=14) [data on aspirin and paracetamol+sponging were not extracted]	cited in systematic review of Meremikwa 2003
Steele, 1970, USA	Experimental: randomized controlled trials	130 children aged 6 months to 5 years with a rectal temperature of 39.4°C or more	1. Placebo (n=15) 2. Tepid water sponging + placebo (n=15) 3. Paracetamol alone (n=25) 4. Tepid sponging + paracetamol (n=25) 5. Iced water + paracetamol (n=25) 6. Alcohol in water + paracetamol (n=25) [data on physical methods + paracetamol were not extracted]	cited in systematic review of Meremikwa 2003

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Temperature difference	Cold water sponging vs paracetamol	@ 30 minutes: Statistically significant: 1.63±0.92 vs 0.56±0.74 MD: 1.10, 95%CI [0.74; 1.46] (p<0.00001)* *In favour of cold water sponging*	1, 41 vs 43	Aluka, 2013
		@ 60 minutes: Not statistically significant: 0.93±0.80 vs 0.97±0.67 MD: -0.04, 95%CI [-0.36; 0.28] (p=0.80)*		
		@ 90 minutes: Statistically significant: 0.55±0.94 vs 1.38±0.71 MD: -0.83, 95%CI [-1.19; -0.47] (p<0.00001)* *In favour of paracetamol*	1, 40 vs 43	
		@120 minutes Statistically significant: 0.39±0.83 vs 1.60±0.60 MD: -1.21, 95%CI [-1.53; -0.89] (p<0.00001)* *In favour of paracetamol*	1, 38 vs 42 §	
Responding at 1 hour	Tepid sponging vs placebo	Not statistically significant: 1/14 vs 0/6*	1, 14 vs 6 §	Hunter 1973

		RR: 1.40, 95%CI [0.06; 30.23] (p=0.83)* ¥		
	Tepid sponging vs paracetamol alone	Not statistically significant: 1/14 vs 2/12 RR: 0.43, 95%CI [0.04; 4.16] (p=0.47)* ¥	1, 14 vs 12 §	
Responding at 2 hours	Tepid sponging vs placebo	Not statistically significant: 6/14 vs 0/6 RR: 6.07, 95%CI [0.39; 93.29] (p=0.20)* ¥	1, 14 vs 6 §	
	Tepid sponging vs paracetamol alone	Not statistically significant: 6/14 vs 10/12 RR: 0.51, 95%CI [0.27; 0.99] (p=0.05)*	1, 14 vs 12 §	
Resolution of fever by 1 hour	Tepid water sponging vs placebo	Not statistically significant: 2/15 vs 0/15 RR: 5.00, 95%CI [0.26; 96.13] (p=0.29) ¥	1, 15 vs 15 §	Steele, 1970
	cold water sponging vs paracetamol	Not statistically significant: 12/41 vs 18/43 OR: 0.57, 95%CI [0.23; 1.42] (p=0.23) ¥	1, 41 vs 43	Aluka, 2013
Resolution of fever by 2 hours	Tepid water sponging vs placebo	Statistically significant: 8/15 vs 0/15 RR: 17.00, 95%CI [1.07; 270.41] (p=0.045) *In favour of tepid water sponging*	1, 15 vs 15 §	Steele, 1970
	cold water sponging vs paracetamol	Statistically significant: 4/38 vs 33/42 OR: 0.03, 95%CI [0.01; 0.11] (p<0.00001)* *In favour of paracetamol*	1, 38 vs 42 §	Aluka, 2013
Discomfort (shivering, pallor, cyanosis, "goose flesh")	Tepid water sponging vs placebo	Not statistically significant: 5/15 vs 2/15 RR: 2.50, 95%CI [0.57; 10.93] (p=0.22) ¥	1, 15 vs 15 §	Steele, 1970
	Tepid water sponging vs paracetamol	Not statistically significant: 2/15 vs 1/15 RR: 2.00, 95%CI [0.20; 19.78] (p=0.55) ¥*		
Discomfort – shivering	cold water sponging vs paracetamol	Statistically significant: 11/44 vs 0/44 OR: 30.55, 95%CI [1.74; 537.07] (p=0.02)* *In favour of paracetamol*	1, 44 vs 44	Aluka, 2013
Discomfort – Crying		Statistically significant: 14/44 vs 2/44 OR: 9.80, 95%CI [2.07; 46.35] (p=0.004)* *In favour of paracetamol*		

Mean ± SD (unless otherwise indicated)

* Calculations done by the reviewer(s) using Review Manager software

¥ Imprecision (large variability of results)

§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Aluka, 2013	No, allocation sequence and concealment through balloting	No, but not possible	Yes, loss to follow up, but not mentioned in article	No	
Hunter, 1973	Unclear, not mentioned	Unclear, not mentioned	No, loss to follow-ups were documented	No	
Steele, 1970	Unclear, not mentioned	Unclear, not mentioned	No	No	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	see table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/large variability of results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	**Sponging vs placebo** There is limited evidence from 2 experimental studies (extracted from 1 systematic review), neither in favour of the intervention nor the control. A statistically significant increase of resolution of fever at 1 hours, using tepid water sponging compared to placebo, could not be demonstrated (Hunter 1973). However, it was shown that tepid water sponging resulted in a statistically significant increase of resolution of fever at 2 hours compared to placebo (Steele 1970). A statistically significant difference in discomfort, using tepid water sponging compared to placebo, could not be demonstrated (Steele 1970). Evidence is of low quality and results of these studies are imprecise due to limited sample size and/or large variability of results. **Sponging vs paracetamol** <u>Tepid water sponging vs paracetamol</u> There is limited evidence from 2 experimental studies (extracted from 1 systematic review), neither in favour of the intervention nor the control. A statistically significant increase of resolution of fever at 1 or 2 hours, using tepid water sponging compared to paracetamol, could not be demonstrated (Hunter 1973). A statistically significant difference in discomfort, using tepid water sponging compared to paracetamol, could not be demonstrated (Steele 1970). Evidence is of low quality and results of these studies are imprecise due to limited sample size and/or large variability of results. <u>Cold water sponging vs paracetamol</u> There is limited evidence from 1 experimental study in favour of paracetamol. (In making this evidence conclusion, we place a higher value on the totality of the results over significant outcomes one by one). Although it was shown that cold water sponging resulted in a statistically significant decrease of temperature after 30 minutes, compared to paracetamol, this trend was not seen at later time points. Furthermore, it was shown that paracetamol resulted in a statistically significant decrease of temperature after 90 and 120 minutes. Moreover, it

	was shown that cold water sponging resulted in a statistically significant increase of discomfort, compared to paracetamol (Aluka, 2013). Evidence is of low quality and results cannot be considered precise due to limited sample size and/or large variability of results.
Reference(s)	**Articles** Aluka TM, Gyuse AN, Udonwa NE, Asibong UE, Meremikwu MM, Oyo-Ita A. *Comparison of cold water sponging and acetaminophen in control of fever among children attending a tertiary hospital in South Nigeria*. Journal of Family Medicine and Primary Care 2013, 2(2):153-158 Hunter J. *Study of antipyretic therapy in current use*. Archives of Disease in Childhood, 48:313-315 Steele RW, Tanaka PT, Lara RP, Bass JW. *Evaluation of sponging and of oral antipyretic therapy to reduce fever*. Journal of Pediatrics 1970, 77(5):824-9 **Systematic reviews** Meremikwu MM, Oyo-Ita A. *Physical methods versus drug placebo or no treatment for managing fever in children.* Cochrane Database of Systematic Reviews 2003, Issue 2. Art. No.:CD004264

Fever – Physical methods + paracetamol (First aid)

Question (PICO)	In children (P), is the use of physical methods (sponging, fanning, bathing) combined with paracetamol (I) compared to no intervention or paracetamol alone or physical methods alone (C) effective as a first aid treatment for fever (O)?
Search Strategy	Databases A Cochrane review "Physical methods versus drug placebo or no treatment for managing fever in children" was identified. An update of the search was performed starting from de end date of the search in de Cochrane review (2005). **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh fever] OR pyrexia:ti,ab,kw OR fever*:ti,ab,kw 2. Spong*:ti,ab,kw OR [mh baths] OR bath*:ti,ab,kw OR fanning:ti,ab,kw OR "physical methods":ti,ab,kw OR cool*:ti,ab,kw 3. 1-2 AND [filter 2005-2015] **MEDLINE** (via PubMed interface) for systematic reviews and meta-analyses using the following search strategy: 1. "fever"[Mesh] OR fever*[TIAB] OR "pyrexia"[TIAB] 2. Sponging[TIAB] OR baths[Mesh] OR bath*[TIAB] OR fanning[TIAB] OR "physical methods"[TIAB] OR cool*[TIAB] 3. Child[Mesh] OR child*[TIAB] 4. 1-3 AND [filter 2005 – 2015] **Embase** (via Embase.com interface) using the following search strategy: 1. Fever/exp OR fever*:ab,ti OR pyrexia:ab,ti 2. Sponging:ab,ti OR bath/exp OR bath*:ab,ti OR fanning:ab,ti OR 'physical methods':ab,ti OR cool*:ab,ti 3. Child/exp OR child*:ab,ti 4. 1-3 AND [filter 2005-2015] Guidelines, systematic reviews, retrieved with the above searches, and used as source for individual studies: Meremikwu, 2003

	Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in MEDLINE (via PubMed interface).
Search date	29 May 2015
In/Exclusion criteria	**Population**: Include: sick or injured children with fever. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Studies on the use of fanning, bathing (in tepid/warm/ice water or in alcohol combined with water) or sponging (tepid/warm/ice water) combined with paracetamol as a treatment for fever. Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. Studies on the use of only physical methods or paracetamol alone. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Meremikwu, 2003, Nigeria	Systematic review	7 studies including 467 children with fever	Physical methods (tepid sponging or sponging with a mixture of alcohol (70% isopropylalcohol and water) + paracetamol vs control (paracetamol only or placebo)	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Number with temperature fall of 1.5°C by 1 hour	Tepid sponging + paracetamol vs paracetamol alone	Not statistically significant: 2/13 vs 2/12 RR: 0.92 [0.15; 5.56] (p=0.93) ¥	1, 14 vs 12 §	Meremikwu 2003
Number with temperature fall of 1.5°C by 2 hours	Tepid sponging + paracetamol vs paracetamol alone	Not statistically significant: 11/13 vs 10/12 RR: 1.02, 95%CI [0.72; 1.43] (p=0.93) ¥	1, 14 vs 12 §	

Resolution of fever by 1 hour	Tepid sponging + paracetamol vs paracetamol	Statistically significant: 26/60 vs 2/65 RR: 11.76, 95%CI [3.39; 40.79], (p=0.0001) *In favour of tepid sponging + paracetamol*	2, 60 vs 65 §	
Resolution of fever by 2 hours		Statistically significant: 23/25 vs 17/25 RR: 1.35, 95%CI [1.01; 1.81] (p=0.043) *In favour of tepid sponging + paracetamol*	1, 25 vs 25 §	
Mean temperature change		Not statistically significant: 1.06±0.61 vs 0.92±0.57 MD: 0.14, 95%CI [-0.06; 0.34] (p=0.18)	1, 73 vs 57 §	
Adverse events (vasomotor change, shivering, gross signs of discomfort)		Statistically significant: 14/70 vs 2/75 RR: 5.09, 95%CI [1.56; 16.60], (p=0.007) *In favour of paracetamol only*	3, 70 vs 75 §	
Number with poor comfort score	Alcohol/water sponging + paracetamol vs paracetamol	Statistically significant: 15/25 vs 2/25 RR: 7.50, 95%CI [1.91; 29.44], (p=0.004)* *In favour of paracetamol only*	1, 25 vs 25 §	
	Ice water sponging + paracetamol vs paracetamol	Statistically significant: 15/25 vs 2/25 RR: 7.50, 95%CI [1.91; 29.44], (p=0.004)* *In favour of paracetamol only*		

* Calculations done by the reviewer(s) using Review Manager software
¥ Imprecision (large variability of results)
§ Imprecision (limited sample size or low number of events)

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	see systematic review Meremikwu 2003
Imprecision	-1	Limited sample sizes/large variability of results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	**Resolution of fever** There is limited evidence from 1 systematic review in favour of sponging with tepid water combined with paracetamol. (In making this evidence conclusion, we place a higher value on statistically significant outcomes of bigger studies over not statistically significant outcomes of smaller studies) It was shown that sponging with tepid water combined with paracetamol resulted in a statistically significant increase of resolution of fever by 1 hour and by 2 hours, compared to paracetamol only (Meremikwu 2003). However, a statistically significant increase of children with a temperature fall of 1.5°C by 1 hour or by 2 hours, using sponging with tepid water combined with paracetamol compared to paracetamol only, could not be demonstrated (Meremikwu 2003).

	Evidence is of low quality and results cannot be considered precise due to limited sample size and/or large variability of results. **Adverse events/discomfort** There is limited evidence from 1 systematic review in favour of paracetamol only. It was shown that sponging with tepid water combined with paracetamol resulted in a statistically significant increase of adverse events, compared to paracetamol only. It was also shown that alcohol combined with paracetamol or ice water combined with paracetamol resulted in a statistically significant increase of number of children with a poor comfort score (Meremikwu 2003). Evidence is of low quality and results cannot be considered precise due to limited sample size and/or large variability of results.
Reference(s)	**Systematic reviews** Meremikwu MM, Oyo-Ita A. *Physical methods versus drug placebo or no treatment for managing fever in children.* Cochrane Database of Systematic Reviews 2003, Issue 2. Art. No.:CD004264

Sexually transmitted diseases – Condoms (Prevention)

Question (PICO)	In people (P), is the use of condoms (I) effective to prevent sexually transmitted diseases (O) compared to no condoms (C)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews) using the following search strategy: 1. [mh sexually transmitted diseases] OR [mh acquired immunodeficiency syndrome] OR [mh HIV] OR [mh syphilis] OR [mh hepatitis B] OR [mh gonorrhea] OR [mh chlamydia] OR "sexually transmitted disease":ti,ab,kw OR "sexually transmitted diseases":ti,ab,kw OR aids:ti,ab,kw OR HIV:ti,ab,kw OR syphilis:ti,ab,kw OR hepatitis B:ti,ab,kw OR gonorrh*:ti,ab,kw OR chlamydia:ti,ab,kw 2. [mh condoms] OR condom*:ti,ab,kw 3. 1 AND 2 **MEDLINE** (via PubMed interface) for guidelines and systematic reviews using the following search strategy: 1. "Sexually transmitted diseases" [Mesh] or "Acquired immunodeficiency syndrome"[Mesh] OR Syphilis[Mesh] OR Hepatitis B[Mesh] OR Gonorrhea[Mesh] OR chlamydia[Mesh] OR HIV[Mesh] OR "Sexually transmitted disease"[TIAB] OR "Sexually transmitted diseases"[TIAB] OR AIDS[TIAB] OR HIV[TIAB] OR Syphilis[TIAB] OR Hepatitis B[TIAB] OR Gonorrh*[TIAB] OR chlamydia[TIAB] 2. "Condoms"[Mesh] OR condom*[TIAB] 3. "Guideline "[Publication Type] OR "Practice Guidelines as Topic"[Mesh] OR "Practice Guideline "[Publication Type] OR practice guideline*[TIAB] OR Meta-Analysis as Topic[Mesh] OR meta analy*[TIAB] OR metaanaly*[TIAB] OR Meta-Analysis[Publication Type] OR systematic review*[TIAB] OR systematic overview*[TIAB] OR Review Literature as Topic[Mesh] OR cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB] OR reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB] OR selection criteria[TIAB] OR data extraction[TIAB] AND Review[PT] 4. 1-3 AND **Embase** (via Embase.com interface) for guidelines and systematic reviews using the following search strategy: 1. 'sexually transmitted disease'/exp OR 'acquired immune deficiency syndrome'/exp OR 'human immunodeficiency virus'/exp OR Syphilis/exp OR Hepatitis B/exp OR

	gonorrhea/exp OR chlamydia/exp OR 'sexually transmitted disease':ab,ti OR 'sexually transmitted diseases':ab,ti OR aids:ab,ti OR 'human immunodeficiency virus':ab,ti OR hiv:ab,ti OR syphilis:ab,ti OR hepatitis B:ab,ti OR gonorrh*:ab,ti OR chlamydia:ab,ti 2. Condom/exp OR condom*:ab,ti 3. 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti 4. 1-3 AND
Search date	4 November 2015
In/Exclusion criteria	**Population**: Include: people with(out) a sexual transmitted disease **Intervention**: Include: condom use **Comparison:** Include: no condom use **Outcome**: Include: direct health outcomes related to sexually transmitted diseases **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies.

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Giannou, 2015, Greece	Systematic review	25 studies (15 prospective cohort studies and 10 case-control or cross-sectional studies) with 10676 HIV serodiscordant heterosexual couples were analysed	Intervention: condom use (always) Control: condom use (never or inconsistent use)	Only data from the 15 prospective cohort studies were extracted. Hughes 2012 (n=3297) only reported relative risk estimates (no number of participants per group)

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
HIV transmission	Condom use (always) vs no condom use (never)	Statistically significant: RR: 0.28, 95%CI [0.18;0.44] (p<0.05) £ *In favour of condom use*	9, 704 vs 464	Giannou, 2015
	Condom use (always) vs rarely/sometimes/never condom use (inconsistent)	Statistically significant: RR: 0.20, 95%CI [0.09;0.44] (p<0.05) £ *In favour of condom use*	9, 4138 vs 1163	

£ No raw data available

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	0	See Systematic review Giannou 2015
Imprecision	0	
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is limited evidence in favour of condom use. It was shown that condom use (always) resulted in a statistically significant decreased HIV transmission, compared to no condom use (Giannou 2015). Evidence is of low quality.
Reference(s)	**Systematic reviews** Giannou FK, Tsiara CG, Nikolopoulos GK, Talias M, Benetou V, Kantzanou M, Bonovas S, Hatzakis A[1]. *Condom effectiveness in reducing heterosexual HIV transmission: a systematic review and meta-analysis of studies on HIV serodiscordant couples*. Expert Rev Pharmacoecon Outcomes Res. 2015,21:1-11.

Sexually transmitted diseases – Alcohol (Risk Factor)

Question (PICO)	In people (P), is alcohol (I) a risk factor for sexually transmitted diseases (O) compared to no alcohol (C)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews) using the following search strategy: 1. [mh sexually transmitted diseases] OR [mh acquired immunodeficiency syndrome] OR [mh HIV] OR [mh syphilis] OR [mh hepatitis B] OR [mh gonorrhea] OR [mh chlamydia] OR "sexually transmitted disease":ti,ab,kw OR "sexually transmitted diseases":ti,ab,kw OR aids:ti,ab,kw OR HIV:ti,ab,kw OR syphilis:ti,ab,kw OR hepatitis B:ti,ab,kw OR gonorrh*:ti,ab,kw OR chlamydia:ti,ab,kw 2. [mh ethanol] OR alcohol*:ti,ab,kw 3. 1 AND 2 **MEDLINE** (via PubMed interface) for guidelines and systematic reviews using the following search strategy: 1. "Sexually transmitted diseases" [Mesh] or "Acquired immunodeficiency syndrome"[Mesh] OR Syphilis[Mesh] OR Hepatitis B[Mesh] OR Gonorrhea[Mesh] OR chlamydia[Mesh] OR HIV[Mesh] OR "Sexually transmitted disease"[TIAB] OR "Sexually transmitted diseases"[TIAB] OR AIDS[TIAB] OR HIV[TIAB] OR Syphilis[TIAB] OR Hepatitis B[TIAB] OR Gonorrh*[TIAB] OR chlamydia[TIAB] 2. Ethanol[Mesh] OR alcohol*[TIAB] 3. "Risk factors"[Mesh] OR risk factor*[TIAB] 4. "Guideline "[Publication Type] OR "Practice Guidelines as Topic"[Mesh] OR "Practice Guideline "[Publication Type] OR practice guideline*[TIAB] OR Meta-Analysis as Topic[Mesh] OR meta analy*[TIAB] OR metaanaly*[TIAB] OR Meta-Analysis[Publication Type] OR systematic review*[TIAB] OR systematic overview*[TIAB] OR Review Literature as Topic[Mesh] OR cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB] OR reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB] OR selection criteria[TIAB] OR data extraction[TIAB] AND Review[PT] 5. 1-4 AND

	Embase (via Embase.com interface) for guidelines and systematic reviews using the following search strategy: 1. 'sexually transmitted disease'/exp OR 'acquired immune deficiency syndrome'/exp OR 'human immunodeficiency virus'/exp OR Syphilis/exp OR Hepatitis B/exp OR gonorrhea/exp OR chlamydia/exp OR 'sexually transmitted disease':ab,ti OR 'sexually transmitted diseases':ab,ti OR aids:ab,ti OR 'human immunodeficiency virus':ab,ti OR hiv:ab,ti OR syphilis:ab,ti OR hepatitis B:ab,ti OR gonorrh*:ab,ti OR chlamydia:ab,ti 2. Alcohol/exp OR alcohol*:ab,ti 3. 'risk factor'/exp OR (risk NEXT/1 factor*):ab,ti 4. 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti 5. 1-4 AND
Search date	4 November 2015
In/Exclusion criteria	**Population**: Include: people with(out) a sexual transmitted disease **Intervention**: Include: alcohol use **Comparison:** Include: no alcohol use **Outcome**: Include: (in)direct health outcomes related to sexually transmitted diseases **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. If both experimental and observational studies are published, only the experimental studies will be included because of higher quality. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies.

Characteristics of included studies

Author, year, Country	Study design	Population	Risk factor	Remarks
Rehm, 2012, Canada	Systematic review (and meta-analysis)	12 randomized controlled trials (n=1518, mean age 23.9±3.2 years) examining the association between blood alcohol content and self-perceived likelihood of using a condom during intercourse	Intervention: alcohol use Control: no alcohol use	

Synthesis of findings

Outcome	Risk factor	Effect Size	#studies, # participants	Reference
Likelihood of engaging in unprotected sex (indicated by a Likert scale and adjusted for publication bias) for an increase in blood alcohol content of 0.1 mg/mL	Alcohol use vs no alcohol use	Statistically significant: Pooled estimate: 2.9%, 95%CI [2.0%;3.9%] (p<0.05) £ *In favour of no alcohol use*	12, 1518 (no information of participants per group)	Rehm, 2012

£ No raw data available

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See Rehm 2012
Imprecision	0	
Inconsistency	0	
Indirectness	-1	Likelihood of engaging in unprotected sex as surrogate for HIV infection
Publication bias	0	
QUALITY (GRADE)	**Final grading Moderate [B]**	

Conclusion	There is evidence in favour of no alcohol use. It was shown that drinking alcohol resulted in a statistically significant increased likelihood of engaging in unprotected sex, compared to no alcohol use (Rehm, 2012). Evidence is of moderate quality.
Reference(s)	**Systematic reviews**Rehm J, Shield KD, Joharchi N, Shuper PA. *Alcohol consumption and the intention to engage in unprotected sex: systematic review and meta-analysis of experimental studies*. Addiction 2012, 107(1):51-59.

Aids – Sterile needles (Prevention)

Question (PICO)	In people (P), is the use of sterile needles (I) effective to prevent HIV transmission (O) compared to using non-sterile needles (C)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh acquired immunodeficiency syndrome] OR [mh HIV] OR aids:ti,ab,kw OR HIV:ti,ab,kw 2. [mh needles] OR needle*:ti,ab,kw 3. [mh disinfection] OR disinfect*:ti,ab,kw 4. 1-3 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Acquired immunodeficiency syndrome"[Mesh] OR HIV[Mesh] OR AIDS[TIAB] OR HIV[TIAB] 2. Needles[Mesh] OR needle*[TIAB] 3. Disinfection[Mesh] OR disinfect*[TIAB] OR sterile[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'Acquired immune deficiency syndrome'/exp OR 'human immunodeficiency virus'/exp OR aids:ab,ti OR 'human immunodeficiency virus':ab,ti OR hiv:ab,ti 2. Needle/exp OR needle*:ab,ti 3. Disinfection/exp OR disinfect*:ab,ti OR sterile:ab,ti 4. 1-3 AND
Search date	5 November 2015
In/Exclusion criteria	**Population**: Include: people (injected drug users) with(out) AIDS. **Intervention**: Include: sterile needle use (whether or not implemented in a needle and syringe programme) **Comparison:** Include: no sterile needle use **Outcome**: Include: direct health outcomes related to HIV transmission **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched.

	An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series**,** animal studies, *ex vivo* or *in vitro* studies.

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Aspinall, 2014, UK	Systematic review	12 studies (1 case-control study, 10 cohort studies and 1 cross-sectional study) comprising at least 12000 person-years of follow-up to assess the association between needle and syringe programmes and HIV transmission.	Intervention: exposure to needle and syringe programmes (i.e. programmes providing people who inject drugs with injecting equipment) Control: no/less exposure to needle and syringe programmes	Only data from the studies with high quality (Newcastle-Ottawa score ≥6) were extracted

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Risk of HIV	Needle and syringe programmes vs no/less needle and syringe programmes	Statistically significant: Pooled RR: 0.42, 95%CI [0.22;0.81] (p<0.001) £ *In favour of needle and syringe programmes (sterile needles)*	5, mix of information on number of HIV seroconversions per persons or person years (see table 2) †	Aspinall, 2014

£ No raw data available

† Imprecision (lack of data)

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	0	
Imprecision	-1	Lack of data
Inconsistency	0	
Indirectness	-1	Needle and syringe programmes as surrogate outcome for sterile needle use
Publication bias	-1	See Aspinall 2014
QUALITY (GRADE)	**Final grading Very Low [D]**	

Conclusion	There is limited evidence in favour of needle and syringe programmes (i.e. use of sterile needles). It was shown that needle and syringe programmes resulted in a statistically significant decreased risk of HIV transmission, compared to no/less needle and syringe programming (Aspinall 2014). Evidence is of very low quality and results cannot be considered precise due to lack of data.
Reference(s)	**Systematic reviews** Aspinall EJ, Nambiar D, Goldberg DJ, Hickman M, Weir A, Van Velzen E, Palmateer N, Doyle JS, Hellard ME, Hutchinson SJ. *Are needle and syringe programmes associated with a reduction in HIV transmission among people who inject drugs: a systematic review and meta-analysis.* Int J Epidemiol. 2014, 43(1):235-248.

Transmission of infections – Barrier for resuscitation (Prevention)

Question (PICO)	In humans (P), is the use of a face shield or a pocket mask for resuscitation (I) compared to mouth-to-mouth ventilation (C) effective to prevent transmission of infections (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: faceshield:ti,ab,kw OR "face shield":ti,ab,kw OR "pocket mask":ti,ab,kw **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Disease Transmission, Infectious"[Mesh] OR transmission[TIAB] OR infect*[TIAB] 2. faceshield[TIAB] OR "face shield"[TIAB] OR "pocket mask"[TIAB] OR "pocket masks"[TIAB] OR "rescue mask" [TIAB] OR "rescue mask"[TIAB] OR "resuscitation mask"[TIAB] OR "CPR mask"[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'disease transmission'/exp OR transmission:ab,ti OR infect*:ab,ti 2. faceshield:ab,ti OR 'face shield':ab,ti OR 'pocket mask':ab:ti OR 'pocket masks':ab:ti OR 'rescue mask':ab:ti OR 'rescue masks':ab:ti OR 'CPR mask':ab:ti OR 'CPR masks':ab:ti 3. 1-2 AND
Search date	24 November 2015
In/Exclusion criteria	**Population**: Healthy people or volunteers **Intervention**: Include: barriers (face shield, pocket mask). Exclude: bag-valve. **Comparison**: Include: mouth-to-mouth ventilation. Exclude: pocket mask, face shield or bag-valve. **Outcome**: Include: Transmission of infection, transmission of oral bacterial flora. Exclude: ventilation outcomes, such as ventilation quality, tidal volume, peak airway pressure. **Study design:** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Spread of infection (respiratory viruses) – use of tissues (Prevention)

Question (PICO)	When people sneeze, cough or blow their noses (P) does the use of tissues or handkerchiefs (I) compared with no tissues or handkerchiefs (C) protect bystanders against the spread of infection (O)?
Search Strategy	Databases **GIN, NGC** (guidelines) using the following search strategy:"nasal tissue*" OR "handkerchie*" OR "kleenex" OR ("infection control" AND tissue*) OR ("respiratory infection" AND tissue*) **BestBETs** (best evidence topics) using the following search strategy: "nasal tissue*" OR "handkerchie*" OR "kleenex" OR "infection control" OR "respiratory infection" **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. MeSH descriptor: [Respiratory Tract Infections] explode all trees or sneez*:ti,ab,kw or cough*:ti,ab,kw (Word variations have been searched) or respiratory symptom*:ti,ab,kw (Word variations have been searched) or respiratory infection*:ti,ab,kw (Word variations have been searched). 2. nasal tissue*:ti,ab,kw or handkerchie*:ti,ab,kw or kleenex:ti,ab, 3. MeSH descriptor: [Communicable Diseases] explode all trees or infection*:ti,ab,kw or infect*:ti,ab,kw 4. limit*:ti,ab,kw or prevent*:ti,ab,kw or reduc*:ti,ab,kw or control*:ti,ab,kw 5. 3 and 4 6. 1 and 2 and 5 **MEDLINE** (via PubMed interface) for guidelines, systematic reviews, experimental and observational studies using the following search strategy: 1. "Respiratory Tract Infections"[Mesh] OR sneez*[TIAB] OR cough*[TIAB] OR respiratory symptom*[TIAB] OR respiratory infection*[TIAB] 2. nasal tissue*[TIAB] OR handkerchie*[TIAB] OR kleenex[TIAB] 3. ("Communicable Diseases"[Mesh] OR infection*[TIAB] OR infective[TIAB] OR infectious[TIAB]) AND (interrupt*[TIAB] OR decreas*[TIAB] OR limit*[TIAB] OR prevent*[TIAB] OR reduce[TIAB] OR reducing[TIAB] OR reduction[TIAB] OR control[TIAB] OR controls[TIAB] OR controlling[TIAB]) **Embase** (via Embase.com interface) using the following search strategy: 1. 'respiratory tract infection'/exp OR sneez*:ab,ti OR cough*:ab,ti OR 'respiratory symptom':ab,ti OR 'respiratory symptoms':ab,ti OR 'respiratory infection':ab,ti OR 'respiratory infections':ab,ti 2. 'nasal tissue':ab,ti OR 'nasal tissues':ab,ti OR handkerchief:ab,ti OR handkerchieves:ab,ti OR kleenex:ab,ti 3. ('communicable disease'/exp OR infect*:ab,ti) AND (interrupt*:ab,ti OR decreas*:ab,ti OR limit*:ab,ti OR prevent*:ab,ti OR reduc*:ab,ti OR control*:ab,ti) 4. 1 AND 2 AND 5 Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	15 March 2013
In/Exclusion criteria	**Population:** Basic first responders, lay caregivers, community health workers, or healthcare professionals or others caring for or in close proximity with patients were included. Studies assessing the spread of infection during daily activities within living environments (ie. households and University residence halls) were included. Studies of

	dense populations of people from different communities at an event (ie. Hajj religious pilgrimage) were excluded. Animal studies were excluded. **Intervention:** Studies assessing the effects of tissue use to limit the spread of common cold/infection (when sneezing, coughing or blowing one's nose etc) were included. **Comparison:** No use of tissues (when sneezing, coughing or blowing one's nose etc). **Outcome:** Common cold / infection in previously healthy healthcare worker or study participant. **Study design:** For a guideline or review to be included we used the following criteria: the inclusion/exclusion criteria are reported; the search was adequate; the included studies are synthesised; the validity of the included studies was assessed; sufficient details about the individual included studies are presented. **Language:** English, French, Dutch

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Farr, 1988 USA	Experimental: Randomised controlled trial	Participants: 648 persons in 186 families analysed (1,241 persons in 302 families recruited, while 116 were excluded). Standard tissue group: 201 analysed No tissues group: 244 analysed (Virucidal tissues group: 203 analysed)	Use of standard tissues *(saccharin applied uniformly to all three plies of tissue)* vs control *(continuation of normal hygiene practices)* For 24 weeks, participants were asked to use allocated tissues (or continue regular hygiene practices for control group) and keep a daily listing on a symptom recording card.	Two studies were performed to assess the effectiveness of virucidal nose tissues. In Trial 2, there was no "control" group (ie. no tissues or continuation of normal hygiene habits). Therefore only Trial 1 was useful to this current review. Illness definition: at least two respiratory symptoms on the same day, or a single respiratory symptom on two consecutive days (with the exception of sneezing).

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Number of respiratory illnesses	Standard tissues vs No tissues	Not statistically significant: 786/201 vs 879/244 (p=0.16) † Effect size cannot be calculated.	1, 201 vs 244	Farr 1988

† Imprecision (lack of data)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Remarks

Farr 1988	No	No	Yes – modified ITT analysis *(less participants analysed than randomised)*	No	Unable to extract raw data relevant to current question

Level of the body of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See 'Quality of evidence' table.
Imprecision	-1	Data was pulled from two of the 3 study arms and data was missing.
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Very Low [D]**	

Conclusion(s)	There is inconclusive evidence from 1 experimental study on the effect of **tissue** use on the spread of **common respiratory infections** (*no evidence of effect*) (Farr 1988, D). In 1 experimental study the effect of the use of tissues to prevent the spread of infection could not be demonstrated due to lack of data.
Reference(s)	Farr BM, Hendley JO, Kaiser DL, Gwaltney JM. *Two randomized controlled trials of virucidal nasal tissues in the prevention of natural upper respiratory infections.* Am J Epidemiol 1988, 128(5):1162-1172.

Malaria – Sunscreen + Insect repellent (Prevention)

Question (PICO)	In humans (P), is the combined used of sunscreen and insect repellent (I) effective to prevent insect stings (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "insect bites and stings"] OR insect*:ti,ab,kw OR mosquito*:ti,ab,kw OR Culicidae:ti,ab,kw OR Culex:ti,ab,kw 2. [mh "Insect repellents"] OR Repellent*:ti,ab,kw 3. [mh "sunscreening agents"] OR sunscreen*:ti,ab,kw 4. 1-3 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "insect bites and stings"[Mesh] OR insect*[TIAB] OR mosquito*[TIAB] OR Culicidae [TIAB] OR Culex [TIAB] 2. "Insect repellents"[Mesh] OR Repellent*[TIAB] 3. "sunscreening agents"[Mesh] OR sunscreen*[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. insect bite'/exp OR insect*:ab,ti OR mosquito*:ab,ti OR culicidae:ab,ti OR culex:ab,ti 2. 'insect repellent'/exp OR repellent*:ab,ti 3. 'sunscreen'/exp OR sunscreen*:ab,ti 4. 1-3 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	02 November 2015

In/Exclusion criteria	**Population**: Include: healthy volunteers of all ages. **Intervention**: Include: combined use of insect repellents and sunscreen. Exclude: studies on the use of sunscreen or insect repellent alone. **Comparison**: Include: sunscreen alone or insect repellent alone. **Outcome**: Include: efficacy of insect repellent, efficacy of sun protection factor (SPF). Exclude: behavior change, measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Montemarano, 1997, USA	Experimental: Randomized controlled trial	14 volunteers assigned to one of 7 regimens (2 volunteers in each group)	8. Sunscreen alone with SPF after 15 min 9. Sunscreen with insect repellent after 15 min 10. Sunscreen with insect repellent after 45 min 11. Sunscreen with insect repellent after 75 min 12. Sunscreen with insect repellent after 105 min 13. Sunscreen alone with SPF after 105 min 14. Insect repellent alone with SPF after 15 min Sunscreen: Coppertone Sport SPF 15 Insect repellent: polymer formulation containing 33% diethylmethylbenzamide (DEET)	SPF = minimum amount of UVR necessary to produce erythema in a 1 cm^2 area of skin protected with 2 µl sunscreen divided by the amount of UVR necessary to produce erythema in unprotected skin. Sun protection factor (SPF) was measured 15 minutes after application of last substance
Murphy, 2000, USA	Experimental: Randomized controlled trial	20 volunteers. Total number of test iterations was 40. This was obtained by testing two different study formulations (one on each forearm) on 4 volunteers over 5 study days.	1. Control: no sunscreen or insect repellent 2. Insect repellent only 3. Insect repellent applied 5 min before cream sunscreen 4. Cream sunscreen applied 5 min before insect repellent 5. Insect repellent applied 5 min before gel sunscreen	The amount of insect repellent applied was 1.1 mg/cm^2. The amount of sunscreen applied was 2 mg/cm^2. Products were applied on a 21 x 8 cm area on the forearms.

		Test cages contained 15 nulliparous female mosquitoes and were secured with Velcor straps on each forearm. The number of mosquitoes feeding at the end of 90 seconds was recorded. The procedure was repeated at 2, 4, 6, 8 and 10 hours.	6. Gel sunscreen applied 5 min before insect repellent 7. Cream sunscreen only 8. Gel sunscreen only	
Webb, 2009, Australia	Experimental: Randomized controlled trial (within subjects design)	Candidate volunteers each tested one treatment per day. ±1.0 g of test formulation was applied evenly to the forearm. The forearm was then exposed to mosquitoes for 3 min. Total number of landings and total number of bites were recorded.	1. Commercial 80% DEET formulation 2. Commercial 80% DEET formulation + sunscreen formulation 3. Commercial 6.98% DEET formulation 4. Commercial 7.14% DEET formulation + sunscreen with insect repellent 5. Commercial 17% DEET formulation 6. Commercial 17% DEET formulation + concurrent reapplication of sunscreen 7. Untreated control Sunscreen formulation used was 30+ SPF [only data on repellent alone vs repellent + sunscreen were extracted]	For combined repellent + sunscreen testing, forearms were exposed for 3 min (treated) or 1 min (untreated) every 60 min until three bites were recorded. For the testing of concurrent DEET and sunscreen usage, repellent was applied to the forearms of volunteers as described and then 1.0 g sunscreen was applied over the top at a recommended reapplication rate (2 h).

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
SPF	sunscreen with insect repellent (after 15-75 min) vs sunscreen alone with SPF after 15 min	Statistically significant: 12.45 vs 18.7 MD: 6.25 Mean decrease of 33.5% p<0.001£ *In favour of sunscreen alone*	1, 8 vs 2 §	Montemarano, 1997
	sunscreen with insect repellent (after 105 min) vs sunscreen alone with SPF after 105 min	13.5 vs 18.8 £† MD: 5.3 Mean decrease of 28% no p-value available	1, 2 vs 2 §	
Mean repellency level (%)	insect repellent + sunscreen vs insect repellent alone	Not statistically significant: After 0-2-4 hours: 100% vs 100% MD: 0 (p>0.05) £†	1, 4 vs 1 §	Murphy, 2000

		After 6 hours: 100% vs 98* MD: 2 (p>0.05) £† After 8 hours: 99% vs 95% MD: 4 (p>0.05) £† After 10 hours: 98% vs 92% MD: 6 (p>0.05) £†		
Mean Protection Time (MPT, min)	80% DEET + sunscreen vs 80% DEET	Not statistically significant: 830±20.2 vs 770±54.8 MD: 60 (p=0.286) ££†	1 (exact number of participants not mentioned) (within subjects design)	Webb, 2009
	7.14% DEET + sunscreen vs 6.98% DEET only	Not statistically significant: 240±15.5 vs 230±18.4 MD: 10 (p=0.687) ££†		
	17% DEET + reapplication sunscreen vs 17% DEET alone	Statistically significant: 330±25.2 vs 400±12.7 MD: -70 (p=0.036) ££ *In favour of DEET alone*		

Outcome measures expressed as Means
£ No SD's and CI available
†† No CI available
† Imprecision (lack of data)
§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Montemarano, 1997	Unclear, not mentioned	Unclear, not mentioned	No	No	
Murphy, 2000	Unclear, not mentioned	Unclear, not mentioned	No	No	
Webb, 2009	Unclear, randomized, but not mentioned how	Unclear, not mentioned	No	No	within subjects design

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/lack of data
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	**Efficacy of sunscreen** There is limited evidence from 1 experimental study in favour of sunscreen alone. It was shown that sunscreen combined with insect repellent resulted in a statistically significant decrease of sun protection factor, compared to sunscreen alone (Montemarano 1997). Evidence is of low quality and results cannot be considered precise due to limited sample size and lack of data. **Efficacy of insect repellent**

	There is limited evidence neither in favour of the intervention nor the control. A statistically significant decrease of repellency, using the combined use of insect repellent and sunscreen compared to insect repellent alone, could not be demonstrated (Murphy 2000, Webb 2009). However, it was shown that insect repellent combined with repeated application of sunscreen resulted in a statistically significant decrease of mean protection time, compared to insect repellent alone (Webb 2009). Evidence is of low quality and results of these studies are imprecise due to limited sample size and lack of data.
Reference(s)	**Articles** Montemarano AD, Gupta RK, Burge JR, Klein K. *Insect repellents and the efficacy of sunscreens*. Lancet 1997, 349:1670-1671 Murphy ME, Montemarano AD, Debboun M, Gupta R. *The effect of sunscreen on insect repellent: a clinical trial*. J Am Acad Dermatol 2000, 43:219-22 Webb CE, Russell RC. *Insect repellents and sunscreen protection strategies against mosquito-borne disease*. Aust N Z J Public Health 2009, 33:485-90

Malaria – Indoor Residual Spraying (IRS) (Prevention)

Question (PICO)	In humans (P), is the use of indoor residual spraying (I) effective to prevent insect stings (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews) using the following search strategy: "indoor residual spray*":ti,ab,kw OR "house spray*":ti,ab,kw One Cochrane review was identified on this topic: Pluess 2010. An extra search was performed to search for individual studies between September 2009 (= end date search Cochrane review) and November 2015 using the following search strategies: The **Cochrane Library** (controlled trials) using the following search strategy: 1. [mh "insect bites and stings"] OR insect*:ti,ab,kw OR mosquito*:ti,ab,kw OR Culicidae:ti,ab,kw OR Culex:ti,ab,kw OR malaria:ti,ab,kw 2. "indoor residual spray*":ti,ab,kw OR "house spray*":ti,ab,kw 3. 1-2 AND Publication Year: 2009-2015 **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "insect bites and stings"[Mesh] OR insect*[TIAB] OR mosquito*[TIAB] OR Culicidae [TIAB] OR Culex [TIAB] OR malaria[TIAB] 2. "indoor residual spray*"[TIAB] OR "house spray*"[TIAB] 3. 1-2 AND Publication date: 01/09/2009 – 04/11/2015 **Embase** (via Embase.com interface) using the following search strategy: 1. 'insect bite'/exp OR insect*:ab,ti OR mosquito*:ab,ti OR culicidae:ab,ti OR culex:ab,ti 2. ('indoor residual' NEXT/1 spray*):ab,ti OR (house NEXT/1 spray*):ab,ti 3. 1-2 AND Publication years: 2009-2015 Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	03 November 2015

In/Exclusion criteria	**Population**: Children and adults living in rural and urban malarious areas. **Intervention**: Include: Indoor residual spraying (IRS). Exclude: combined IRS and ITN. **Comparison**: Include: no IRS or insecticide-treated nets (ITN) **Outcome**: Include: Incidence of re-infections, parasite incidence, parasite prevalence, mosquito mortality, blood feeding inhibition. **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline)

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Akogbeto, 2011, Benin	Experimental: Non-randomized controlled trial	4 districts of Oueme Department in Benin. First 3 districts are characterized by the presence of two types of environment: (1) plateau zone far from flooding areas (indoor residual spraying (IRS) arm): 2 rounds of IRS were carried out (July 2008 and March 2009) and (2) a swampy zone on the border of the Oueme River and Lake Nokoue (long-lasting insecticide-impregnated net (LLIN) arm): 48819 LLINs were distributed in October 2008 and May 2009 to 47524 households.	1. IRS: bendiocarb at a dose of 400 mg/m^2 2. LLIN (Permanet 2.0) 3. Control area: no intervention [Data of LLIN vs control were not extracted]	
Kitau, 2014, Tanzania	Experimental: Randomized controlled trial	Adult volunteers slept in experimental huts in which the inner walls were covered with wooden panels on which the respective IRS treatments were applied. A suite of 6 huts were used for the trial. Sleepers rotated between huts after each trial night to reduce any bias due to differences in individual attractiveness to mosquitoes. Treatments were rotated between huts every 7 days. Mosquito species used: *Anopheles arabiensis* and *Culex quinquefasciatus*.	1. IRS treatment 1: DEET MC 8 g/m^2 2. IRS treatment 2: Lambdacyhalothrin CS 0.025 g/m^2 3. IRS treatment 3: Permethrin EC 0.5 g/m^2 4. IRS treatment 4: Pirimiphos methyl CS 1 g/m^2 5. IRS treatment 5: DDT WP 2 g/m^2 6. Untreated control	

Pluess, 2010, Switzerland	Systematic review (Cochrane review)	6 studies (4 RCT, 1 controlled before-after study, 1 interrupted time series) including participants of all ages	IRS vs no IRS IRS vs ITN	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Human biting rate decrease (%)	IRS vs LLIN	Statistically significant: district Adjohoun: 73.66 vs 50.63 MD: 23.03 (p<0.05) ££ *In favour of IRS* Statistically significant: district Dangbo: 95.22 vs 72.6 MD: 22.62 (p<0.05) ££ *In favour of IRS*	1, exact number not mentioned †	Akogbeto, 2011
Anopheles arabiensis mortality	IRS treatment 1 (DEET) vs untreated control	Statistically significant: 298/362 vs 13/165 OR: 54.44, 95%CI [29.07; 101.96] (p<0.00001)* *In favour of DEET*	1, 362 vs 165 (=numbers of entered mosquitoes)	Kitau, 2014
	IRS treatment 2 (Lambda-cyhalothrin) vs untreated control	Statistically significant: 265/348 vs 13/165 OR: 37.33, 95%CI [20.13; 69.24] (p<0.00001)* *In favour of lambda-cyhalothrin*	1, 348 vs 165 (=numbers of entered mosquitoes)	
	IRS treatment 3 (Permethrin) vs untreated control	Statistically significant: 319/415 vs 13/165 OR: 38.85, 95%CI [21.10; 71.55] (p<0.00001)* *In favour of Permethrin*	1, 415 vs 165 (=numbers of entered mosquitoes)	
	IRS treatment 4 (Pirimiphos methyl) vs untreated control	Statistically significant: 263/306 vs 13/165 OR: 71.51, 95%CI [37.27; 137.22] (p<0.00001)* *In favour of Pirimiphos methyl*	1, 306 vs 165 (=numbers of entered mosquitoes)	
	IRS treatment 5 (DDT) vs untreated control	Statistically significant: 237/292 vs 13/165 OR: 50.38, 95%CI [26.62; 95.34] (p<0.00001)* *In favour of DDT*	1, 237 vs 165 (=numbers of entered mosquitoes)	
Culex quinquefasciatus mortality	IRS treatment 1 (DEET) vs untreated control	Statistically significant: 34/117 vs 6/109 OR: 7.03, 95%CI [2.82; 17.55] (p<0.0001)* *In favour of DEET*	1, 362 vs 165 (=numbers of entered mosquitoes)	
	IRS treatment 2 (Lambda-cyhalothrin) vs untreated control	Statistically significant: 27/62 vs 6/109 OR: 13.24, 95%CI [5.05; 34.73] (p<0.00001)* *In favour of lambda-cyhalothrin*	1, 62 vs 109 (=numbers of entered mosquitoes)	
	IRS treatment 3 (Permethrin) vs untreated control	Statistically significant: 47/84 vs 6/109	1, 84 vs 109 (=numbers of	

		OR: 21.81, 95%CI [8.61; 55.21] (p<0.00001)* *In favour of Permethrin*	entered mosquitoes)	
	IRS treatment 4 (Pirimiphos methyl) vs untreated control	Statistically significant: 51/76 vs 6/109 OR: 35.02, 95%CI [13.52; 90.74] (p<0.00001)* *In favour of Pirimiphos methyl*	1, 51 vs 109 (=numbers of entered mosquitoes)	
	IRS treatment 5 (DDT) vs untreated control	Statistically significant: 70/100 vs 6/109 OR: 40.06, 95%CI [15.84; 101.28] (p<0.00001)* *In favour of DDT*	1, 70 vs 109 (=numbers of entered mosquitoes)	
Blood feeding inhibition (%) (*Anopheles arabiensis*)	IRS treatment 1 (DEET) vs untreated control	Statistically significant: 44 vs 0 MD: 44 (p<0.002) £† *In favour of DEET*	1, no exact numbers available	
	IRS treatment 2 (Lambda-cyhalothrin) vs untreated control	Statistically significant: 35 vs 0 MD: 35 (p<0.002) £† *In favour of Lambda-cyhalothrin*		
	IRS treatment 3 (Permethrin) vs untreated control	Statistically significant: 35 vs 0 MD: 35 (p<0.002) £† *In favour of Permethrin*		
	IRS treatment 4 (Pirimiphos methyl) vs untreated control	Not statistically significant: 2 vs 0 MD: 2 (p>0.05) £†		
	IRS treatment 5 (DDT) vs untreated control	Statistically significant: 41 vs 0 MD: 41 (p<0.002) £ *In favour of DDT*		
Blood feeding inhibition (%) (*Culex quinquefasciatus*)	IRS treatment 1 (DEET) vs untreated control	Not statistically significant: 12 vs 0 MD: 12 (p>0.05) £†	1, no exact numbers available	
	IRS treatment 2 (Lambda-cyhalothrin) vs untreated control	Not statistically significant: 9 vs 0 MD: 9 (p>0.05) £†		
	IRS treatment 3 (Permethrin) vs untreated control	Statistically significant: 41 vs 0 MD: 41 (p<0.037) £ *In favour of Permethrin*		
	IRS treatment 4 (Pirimiphos methyl) vs untreated control	Not statistically significant: 24 vs 0 MD: 24 (p>0.05) £†		
	IRS treatment 5 (DDT) vs untreated control	Not statistically significant: 22 vs 0 MD: 22 (p>0.05) £†		
Incidence of reinfection	IRS vs no IRS (stable malaria areas)	Children 1-5 years Statistically significant: 468/3840 vs 1014/3840 RR: 0.46, 95%CI [0.42; 0.51] (p<0.00001)* *In favour of IRS*	1, 3840 vs 3840	Curtis 1998 (cited in SR Pluess 2010)
	IRS vs ITNs (stable malaria areas)	Children 1-5 years: Statistically significant: 468/3840 vs 384/3840		

		RR: 1.22, 95%CI [1.07; 1.38] (p=0.02)* *In favour of ITNs*		
Parasite incidence	IRS vs no IRS (stable malaria areas)	Children 1-5 years: <u>Statistically significant</u>: 228/413 vs 304/471 RR: 0.86, 95%CI [0.77; 0.95] (p=0.005)* *In favour of IRS* Children >5 years: Not statistically significant: 381/1007 vs 365/984 RR: 1.02, 95%CI [0.91; 1.15] (p=0.73)*	1, 413 vs 471 1, 1007 vs 984	Curtis 1998 (cited in SR Pluess 2010)
	IRS vs no IRS (unstable malaria areas)	All ages: <u>Statistically significant</u>: 1497/44042 vs 2195/44351 RR: 0.69, 95%CI [0.64; 0.73] (p<0.00001)* *In favour of IRS*	1, 44042 vs 44351	Misra 1999 (cited in SR Pluess 2010)
		All ages: <u>Statistically significant</u>: 69/11694 vs 317/6567 aRR: 0.12, 95%CI [0.04; 0.31] (p<0.05)* *In favour of IRS*	1, 11694 vs 6567	Rowland 2000 (cited in SR Pluess 2010)
	IRS vs ITNs (stable malaria areas)	Children 1-5 years: <u>Statistically significant</u>: 228/413 vs 255/405 RR: 0.88, 95%CI [0.78; 0.98] (p=0.02)* *In favour of IRS* Children >5 years: Not statistically significant: 382/1007 vs 346/893 RR: 0.98, 95%CI [0.87; 1.10] (p=0.72)*	1, 413 vs 405 1, 1007 vs 893	Curtis 1998 (cited in SR Pluess 2010)
	IRS vs ITNs (unstable malaria areas)	All ages: <u>Statistically significant</u>: 1497/44042 vs 1014/44158 RR: 1.48, 95%CI [1.37; 1.60] (p<0.00001)* *In favour of ITNs*	1, 44042 vs 44158	Misra 1999 (cited in SR Pluess 2010)
		All ages: Not statistically significant: 1814/7649 vs 966/5450 aRR: 1.34, 95%CI [0.77; 2.70] (p>0.05)*¥	1, 7649 vs 5450	Mnzava 2001 (cited in SR Pluess 2010)
Parasite prevalence	IRS vs no IRS (stable malaria areas)	Children 1-5 years: Not statistically significant: 135/212 vs 135/212 RR: 0.94, 95%CI [0.82; 1.08] (p=0.40)*	1, 212 vs 212	Curtis 1998 (cited in SR Pluess 2010)
	IRS vs no IRS (unstable malaria areas)	All ages: <u>Statistically significant</u>: 84/26084 vs 119/26589	1, 26084 vs 26589	Misra 1999 (cited in SR Pluess 2010)

		RR: 0.72, 95%CI [0.54; 0.95] (p=0.02)* *In favour of IRS*		
		Children 5-15 years: Statistically significant: 41/1528 vs 94/831 RR: 0.24, 95%CI [0.17; 0.34] (p<0.00001)* *In favour of IRS*	1, 1528 vs 831	Rowland 2000 (cited in SR Pluess 2010)
	IRS vs ITNs (stable malaria areas)	Children 1-5 years: Not statistically significant: 135/212 vs 143/237 RR: 1.06, 95%CI [0.91; 1.22] (p=0.47)*	1, 212 vs 237	Curtis 1998 (cited in SR Pluess 2010)
	IRS vs ITNs (unstable malaria areas)	All ages: Statistically significant: 84/26085 vs 51/26849 RR: 1.70, 95%CI [1.18; 2.44] (p=0.003)* *In favour of ITNs*	1, 26085 vs 26849	Misra 1999 (cited in SR Pluess 2010)

* p-values calculated by the reviewer using Review Manager software
£ No SD's/effect size/CI available
££ No SD or CI available
† Imprecision (lack of data)
¥ Imprecision (large variability of results)

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See Systematic review Pluess 2010
Imprecision	-1	Large variability of results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Moderate [B]**	

Quality of studies

Author, Year	**Lack of allocation concealment**	**Lack of blinding**	**Incomplete accounting of outcome events**	**Selective outcome reporting**	**Other limitations**
Akogbeto, 2011	Yes, not randomized	Yes, not possible (spraying vs nets vs nothing)	No	No	
Kitau, 2014	No, treatment order according to Latin square design.	Unclear, not mentioned	No	No	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Lack of data, low variability of results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	**IRS vs no IRS:** There is limited evidence in favour of IRS. It was shown that IRS resulted in a statistically significant decrease of incidence of reinfection in children between 1 and 5 years, compared to no IRS in stable malaria areas (Curtis 1998, cited in Pluess 2010). In stable malaria areas, it was shown that IRS resulted in a statistically significant decrease of parasite incidence in children between 1 and 5 years, compared to no IRS. However, in children above 5 years old, a statistically significant decrease of parasite incidence, compared to no IRS could not be demonstrated (Curtis 1998, cited in Pluess 2010). In unstable malaria areas, it was shown that IRS resulted in a statistically significant decrease of parasite incidence in all age groups, compared to no IRS (Misra 1999 and Rowland 2000, cited in Pluess 2010). In unstable malaria areas, it was shown that IRS resulted in a statistically significant decrease of parasite prevalence, compared to no IRS (Misra 1999 and Rowland 2000, cited in Pluess 2010). In stable malaria areas, a statistically significant decrease of parasite prevalence, using IRS compared to no IRS could not be demonstrated (Curtis 1998, cited in Pluess 2010). It was shown that IRS (different formulations) resulted in a statistically significant increase of *Anopheles arabiensis* and *Culex quinquefasciatus* mortality compared to untreated control (Kitau 2014). It was shown that IRS (DEET, Lambda-cyhalothrin and permethrin) resulted in a statistically significant increase of blood feeding inhibition by *Anopheles arabiensis* compared to untreated control. In *Culex quinquefasciatus* only IRS with permethrin resulted in a statistically significant increase of blood feeding inhibition, compared to untreated control (Kitau 2014). A statistically significant increase of blood feeding inhibition by *Anopheles arabiensis,* using IRS with pirimiphos methyl or DDT compared to untreated control, could not be demonstrated. Also in *Culex quinquefasciatus* a statistically significant increase of blood feeding inhibition using IRS with DEET, lambda-cyhalothrin, pirimiphos methyl or DDT compared to untreated control could not be demonstrated (Kitau 2014). Evidence is of low quality and results cannot be considered precise due to large variability of results and/or lack of data. **IRS vs ITNs:** There is conflicting evidence when comparing IRS vs ITNs. It was shown that IRS (different formulations) resulted in a statistically significant decrease of human biting rate, compared to LLIN (Akogbeto 2011). It was shown that IRS resulted in a statistically significant increase of incidence of reinfection in children between 1 and 5 years, compared to ITNs in stable malaria areas (Curtis 1998, cited in Pluess 2010). In stable malaria areas, it was shown that IRS resulted in a statistically significant decrease of parasite incidence in children between 1 and 5 years, compared to ITNs. However, in children above 5 years old, a statistically significant decrease of parasite incidence, compared to ITNs could not be demonstrated (Curtis 1998, cited in Pluess 2010). In unstable malaria areas, it was shown that ITNs resulted in a statistically significant decrease of parasite incidence, compared to IRS (Misra 1999, cited in Pluess 2010). Furthermore, it was shown that ITNs resulted in a statistically significant decrease of parasite prevalence, compared to IRS (Misra 1999, cited in Pluess 2010). In stable malaria areas, a statistically significant decrease of parasite prevalence, using IRS compared to ITNs could not be demonstrated (Curtis 1998, cited in Pluess 2010) Evidence is of low quality and results cannot be considered precise due to large variability of results and/or lack of data.
Reference(s)	**Articles** Kitau J, Oxborough R, Matowo J, Mosha F, Magesa SM, Rowland M. *Indoor residual spraying with microencapsulated DEET repellent (N,N-diethyl-m-toluamide) for control of* Anopheles arabiensis *and* Culex quinquefasciatus*.* Parasites & Vectors 2014, 7:446.

	Systematic reviews Pluess B, Tanser FC, Lengeler C, Sharp BL. *Indoor residual spraying for preventing malaria*. Cochrane Database of Systematic Reviews 2010, Issue 4. Art. No.: CD006657

Measles – Dabbing eyes with lukewarm water (First Aid)

Question (PICO)	In people with measles (P), is dabbing the eyes with lukewarm water (I) compared to not doing this (C) effective to decrease eye irritation (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Measles"] OR measles:ti,ab,kw 2. [mh "Eye"] OR eye:ti,ab,kw OR [mh "conjunctivitis"] OR conjunctivitis:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Measles"[Mesh] OR measles[TIAB] 2. "Eye"[Mesh] OR eye[TIAB] OR conjunctivitis[TIAB] OR "Conjunctivitis"[Mesh] 3. "Water"[Mesh] OR water[TIAB] OR warm[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'measles'/exp OR measles:ab,ti 2. 'eye'/exp OR eye:ab,ti OR 'conjunctivitis'/exp OR conjunctivitis:ab,ti 3. 'water'/exp OR water:ab,ti OR warm:ab,ti 4. 1-3 AND
Search date	7 October 2015
In/Exclusion criteria	**Population**: Include: people with measles **Intervention**: Include: dabbing the eyes with lukewarm water **Outcome**: Include: eye irritation **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion(s)	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Chickenpox – Dry environment/eosine/menthol powder (First Aid)

Question (PICO)	In people with chickenpox (P), is a dry environment, the use of eosine or menthol powder (I) compared to no dry environment or not using eosine or menthol powder (C) effective to change functional recovery, complications, time to resumption of usual activities, restoration to the pre-exposure condition, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Chickenpox"] OR chickenpox:ti,ab,kw OR varicella:ti,ab,kw 2. [mh "Humidity"] OR [mh "menthol"] OR [mh "Cold temperature"] OR dry:ti,ab,kw OR eosine:ti,ab,kw OR menthol:ti,ab,kw OR cool:ti,ab,kw OR cold:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) using the following search strategy: 1. Chickenpox[TIAB] OR varicella[TIAB] OR "Chickenpox"[Mesh] 2. "Humidity"[Mesh] OR "Menthol"[Mesh] OR "Cold Temperature"[Mesh] OR dry[TIAB] OR eosine[TIAB] OR menthol[TIAB] OR cool[TIAB] OR cold[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'chickenpox'/exp OR chickenpox:ab,ti OR varicella:ab,ti 2. 'humidity'/exp OR 'menthol'/exp OR 'cold'/exp OR dry:ab,ti OR eosine:ab,ti OR menthol:ab,ti OR cool:ab,ti OR cold:ab,ti 3. 1-2 AND
Search date	7 October 2015
In/Exclusion criteria	**Population**: Include: people with chickenpox **Intervention**: Include: keeping the skin dry, go to a cool and dry environment, use eosine to dry the skin, use menthol powder to dry the skin **Outcome**: Include: functional recovery, complications, time to resumption of usual activities, restoration to the pre-exposure condition, time to resolution of symptoms **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion(s)	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Mumps – Warm compresses on ear (First Aid)

Question (PICO)	In people with mumps (P), is putting warm compresses on the ear (I) compared to not doing this (C) effective to decrease pain(O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Mumps"] OR mumps:ti,ab,kw 2. [mh "Hot temperature"] OR heat*:ti,ab,kw OR warm*:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Mumps"[Mesh] OR mumps[TIAB] 2. "Hot temperature"[Mesh] OR heating[Mesh] OR heat*[TIAB] OR warm*[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'mumps'/exp OR mumps:ab,ti 2. 'heat'/exp OR 'heating'/exp OR heat*:ab,ti OR warm*:ab,ti 3. 1-2 AND
Search date	7 October 2015
In/Exclusion criteria	**Population**: Include: people with mumps **Intervention**: Include: putting warm compresses on the ear **Outcome**: Include: pain **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion(s)	No relevant studies were identified using the above search strategy and criteria.

Reference(s)	/

Mumps – Fruit juices (First Aid)

Question (PICO)	In humans with mumps (P), is avoiding fruit juices (I) compared to not avoiding fruit juices (C) effective to prevent more pain (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh Mumps] OR mumps:ti,ab,kw 2. [mh drinking] OR drink*:ti,ab,kw OR liquid*:ti,ab,kw OR juice*:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Mumps[Mesh] OR mumps[TIAB] 2. drinking[Mesh] OR drink*[TIAB] OR liquid*[TIAB] OR juice*[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. mumps/exp OR mumps:ab,ti 2. 'fruit juice'/exp OR juice*:ab,ti OR drinking/exp OR drink*:ab,ti OR liquid*:ab,ti 3. 1-2 AND
Search date	09 November 2015
In/Exclusion criteria	**Population**: People with mumps. **Intervention**: drinking fruit juices **Comparison**: not drinking fruit juices **Outcome**: pain **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Pertussis – Light meal (First Aid)

Question (PICO)	In humans with pertussis who are vomiting (P), is eating light meals (I) compared to not eating light meals (C) effective to change functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh ^vomiting] or vomit*:ti,ab,kw or retch*:ti,ab,kw 2. [mh eating] or [mh meal] or ((light:ti,ab,kw OR digest*:ti,ab,kw) AND meal:ti,ab,kw) 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. vomiting[Mesh:NoExp] or vomit*[TIAB] or retch*[TIAB] 2. eating[Mesh] or meal[Mesh] or ((light[TIAB] OR digest*[TIAB]) AND meal[TIAB]) 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. vomiting/de OR retching/exp OR vomit*:ab,ti OR retch*:ab,ti 2. 'meal'/exp OR (light NEXT/1 meal*):ab,ti OR (digest* NEXT/1 meal*):ab,ti 3. 1-2 AND
Search date	9 November 2015
In/Exclusion criteria	**Population**: people who are vomiting or retching **Intervention**: eating light/easy digestible meals **Comparison**: not eating light meals **Outcome**: Direct health-related outcomes **Study design:** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Croup – Prone position (First aid)

Question (PICO)	In an individual with croup (P), is prone position (I) compared to another position (C) effective to change functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh Croup] OR Croup:ti,ab,kw OR laryngotracheitis:ti,ab,kw OR laryngo-tracheitis:ti,ab,kw 2. [mh "prone position"] OR [mh posture] OR posture:ti,ab,kw OR position*:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Croup[Mesh] OR Croup[TIAB] OR laryngotracheitis[TIAB] OR laryngo-tracheitis[TIAB] 2. "prone position"[Mesh] OR posture[Mesh] OR posture[TIAB] OR position[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Croup/exp OR croup:ab,ti OR laryngotracheitis:ab,ti OR laryngo-tracheitis:ab,ti 2. 'prone position'/exp OR posture/exp OR posture:ab,ti OR position:ab,ti 3. 1-2 AND Guidelines, systematic reviews, retrieved with the above searches, and used as source for individual studies: Clinical Practice Guideline for the Management of Croup in Children, 2007 Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	27 May 2015
In/Exclusion criteria	**Population**: Include: sick children diagnosed with croup. If no studies are found on prone position in children with croup, a systematic review on position in children with acute respiratory distress can be included as indirect evidence. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Studies comparing prone position with another position Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. Adverse events related to intubation. Ventilatory outcomes such as dynamic lung compliance, expiratory resistance, pulmonary resistance and oesophageal pressure. Studies that did not look at prone position. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched.

	An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Gillies, 2012, Australia	Systematic review (Cochrane)	24 studies including 581 preterm or low-weight infants or paediatric patients with acute respiratory distress, aged 2 weeks to 16 years	Prone position vs supine position [only data from prone vs supine position were extracted]	SaO_2: oxygen saturation $PaCO_2$ and PaO_2: arterial blood gases PaO_2/FiO_2: oxygenation indices $tcPCO_2$: transcutaneous PCO_2

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Patients with SaO_2 < 90%	Prone vs supine position	Day 1: Not statistically significant: 1/21 vs 6/21 OR: 0.13, 95%CI [0.01; 1.15] (p=0.07)	1, 21 vs 21 §	Gillies, 2012
		Day2: Not statistically significant: 0/20 vs 3/20 OR: 0.12, 95%CI [0.01; 2.53] (p=0.17) ¥	1, 20 vs 20 §	
Number of episodes with SaO_2<80%		Statistically significant: MD: -3.46, 95%CI [-4.60; -2.33] (p<0.00001) *In favour of prone position*	2, 77 vs 77 § (within subjects)	
SaO_2		Statistically significant: MD: 2.19, 95%CI [1.35; 3.04] (p<0.00001) *In favour of prone position*	8, 165 vs 165 § (within subjects)	
PaO_2		Not statistically significant: 80±19 vs 78±18 MD: 2.00, 95%CI [-5.29; 9.29] (p=0.59)	1, 50 vs 49 §	
		Statistically significant: 71.48±7.51 vs 65.24±7.07 MD: 6.24, 95%CI [2.20; 10.28] (p=0.0002) *In favour of prone position*	1, 25 vs 25 § (within subjects)	
$PaCO_2$		Not statistically significant: 56±13 vs 53±12	1, 50 vs 49 §	

		MD: 3.00, 95%CI [-1.93; 7.93] (p=0.23)		
$tcPCO_2$		Not statistically significant: MD: -2.53, 95%CI [-6.06; 0.99] (p=0.16)	3, 27 vs 27 § (within subjects)	
PaO_2/FiO_2		Not statistically significant: MD: 28.16, 95%CI [-9.92; 66.24] (p=0.15)	2, 61 vs 60 §	
Oxygenation index		<u>Statistically significant:</u> MD: -2.42, 95%CI [-3.60; -1.25] (p=0.000054) *In favour of prone position*		
		Not statistically significant: 30 minutes: 17.05±8.29 vs 17.88±8.15 MD: -0.83, 95%CI [-8.04; 6.38] (p=0.82) Not statistically significant: 2 hours: 14.71±8.56 vs 16.79±6.13 MD: -2.08, 95%CI [-8.04; 6.38] (p=0.53) Not statistically significant: 4 hours: 11.7±5.14 vs 15.9±6.57 MD: -4.20, 95%CI [-9.37; 0.97] (p=0.11) ¥ <u>Statistically significant:</u> 6 hours: 10.26±4.07 vs 15.39±6.96 MD: -5.13, 95%CI [-10.13; -0.13] (p=0.04) *In favour of prone position* <u>Statistically significant:</u> 8 hours: 10.05±4.13 vs 16.94±8.82 MD: -6.89, 95%CI [-12.93; -0.84] (p=0.03) *In favour of prone position* <u>Statistically significant:</u> 12 hours: 9.71±4.27 vs 17.84±10.25 MD: -8.13, 95%CI [-15.01; -1.25] (p=0.02) *In favour of prone position*	1, 10 vs 10 § (within subjects)	
Tidal volume		<u>Statistically significant</u>: 6.2±1.1 vs 6.8±1.0 MD: 0.60, 95%CI [-1.05; -0.15] (p=0.009) *In favour of prone position*	1, 42 vs 42 §	
		Not statistically significant: MD: 0.35, 95%CI [-0.12; 0.82] (p=0.15)	6, 98 vs 98 § (within subjects)	

Minute volume		Not statistically significant: MD: 4.82, 95%CI [-18.01; 27.65] (p=0.68)	6, 98 vs 98 § (within subjects)	
Respiratory rate		Statistically significant: MD: -3.84, 95%CI [-5.93; -1.75], p=0.00031 *In favour of prone position*	2, 111 vs 111 § (within subjects)	
Heart rate		Statistically significant: MD: -7.05, 95%CI [-13.99; -0.10] (p=0.047) *In favour of prone position*	3, 56 vs 57 § (within subjects)	
Adverse events: pressure ulcers		Not statistically significant: 13/51 vs 13/51 OR: 1.00, 95%CI [0.41; 2.44] (p=1.00)	1, 51 vs 51 §	
Adverse events: hypercapnea		Not statistically significant: 1/51 vs 0/51 OR: 3.06, 95%CI [0.12; 76.88] (p=0.50) ¥		
Adverse events: Atelectasis		Not statistically significant: 4/21 vs 9/21 OR: 0.31, 95%CI [0.08; 1.26] (p=0.10) ¥	1, 21 vs 21 §	

Mean ± SD (unless otherwise indicated)
¥ Imprecision (large variability of results)
§ Imprecision (limited sample size or low number of events)

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table systematic review Gillies 2012
Imprecision	-1	Limited sample sizes/large variability of the results
Inconsistency	0	
Indirectness	-1	Studies about acute respiratory distress, not croup specifically + hospitalized infants and children Majority of studies in preterm ventilated infants, only few studies reported data on children older than 1 year of age.
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Conclusion	There is limited evidence from 1 systematic review in favour of prone position. It was shown that prone position resulted in a statistically significant decrease of number of episodes with SaO_2 lower than 80%, oxygenation index (from 6^{th} until 12^{th} hour measurement), tidal volume, respiratory rate and heart rate, and an increase in PaO_2, compared to supine position. These results were all obtained in cross-over trials (Giellis 2012). A statistically significant decrease of patients with SaO_2 below 90%, SaO_2, $PaCO_2$, $tcPCO_2$, PaO_2/FiO_2, minute volume and adverse events, using prone position compared to supine position, could not be demonstrated (Giellis 2012). Evidence is of very low quality and results cannot be considered precise due to limited sample size and/or large variability of results. Furthermore, the evidence is indirect due to hospital setting, mostly premature infants, and most of the patients were intubated during the study.

Reference(s)	**Systematic reviews** Gillies D, Wells D, Bhandari AP. *Positioning for acute respiratory distress in hospitalized infants and children*. Cochrane Database of Systematic Reviews 2012, Issue 7, Art No.: CD003645

Croup – Humidified air (First aid)

Question (PICO)	In an individual with croup (P), is the use of humidified air/steam (I) compared to no intervention (C) effective to change functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh Croup] OR Croup:ti,ab,kw OR laryngotracheitis:ti,ab,kw OR laryngo-tracheitis:ti,ab,kw 2. [mh humidity] OR [mh air] OR humid*:ti,ab,kw OR "cool mist":ti,ab,kw OR [mh steam] OR steam:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Croup[Mesh] OR Croup[TIAB] OR laryngotracheitis[TIAB] OR laryngo-tracheitis[TIAB] 2. Humidity[Mesh] OR Air[Mesh] OR humid*[TIAB] OR "cool mist"[TIAB] OR steam[Mesh] OR steam[TIAB] 3. 1-2 AND [search from 2006 to 2015] (update of Cochrane Review of Moore 2006) **Embase** (via Embase.com interface) using the following search strategy: 1. Croup/exp OR croup:ab,ti OR laryngotracheitis:ab,ti OR laryngo-tracheitis:ab,ti 2. Humidity/exp OR air/exp OR humid*:ab,ti OR 'cool mist':ab,ti OR 'water vapor'/exp OR steam:ab,ti 3. 1-2 AND [search from 2006 to 2015] (update of Cochrane Review of Moore 2006) Guidelines, systematic reviews, retrieved with the above searches, and used as source for individual studies: Johnson, 2013 Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	26 May 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare.

	Outcome: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Moore, 2006, UK	Systematic Review (Cochrane)	135 children with mild to moderate croup, aged 3 months to 6 years	Humidified air vs control (no treatment)	
Scolnik, 2006, Canada	Experimental: randomized controlled trial	140 children presenting at the ED with a diagnosis of croup, with a croup score of 2 or higher. Patients were randomized in a blow-by-humidity group (n=48, mean age 26.8±20.7 months, 34 males and 14 females), a low humidity group (n=46, mean age 25.3±23.2 months, 28 males and 18 females) or a high humidity group (n=46, mean age 23.9±16.7 months, 35 males and 11 females)	High humidity: 100% humidity and water droplets with a mass median diameter of 6.21 µm. Low humidity: 40% relative humidity and 40% oxygen Blow-by-humidity = control group	Sample size was calculated (43 patients per group) based on observing a difference in croup score of 1 between two groups

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Heart rate	Humidified air vs control	Not statistically significant: SMD: -0.18, 95%CI [-8.02; 7.65] (p=0.96)	3, 67 vs 68 §	Moore, 2006
Heart rate (change from baseline)	Blow-by-humidity vs low humidity	After 60 minutes: Not statistically significant: MD: 4.2, 95%CI [-7.0; 15.3] (p>0.05)	1, 48 vs 46	Scolnik, 2006
	High humidity vs blow-by-humidity	After 60 minutes: Not statistically significant:	1, 46 vs 48	

		MD: 6.6, 95%CI [-4.4; 17.6] (p>0.05)		
Respiratory rate	Humidified air vs control	Not statistically significant: SMD: -0.55, 95%CI [-3.20; 2.09] (p=0.68)	3, 67 vs 68 §	Moore, 2006
Respiratory rate (change from baseline)	Blow-by-humidity vs low humidity	After 60 minutes: Not statistically significant: MD: 0.9, 95%CI [-2.6; 4.5] (p>0.05)	1, 48 vs 46	Scolnik, 2006
	High humidity vs blow-by-humidity	After 60 minutes: Not statistically significant: MD: 3.4, 95%CI [-0.1; 6.9] (p>0.05)	1, 46 vs 48	
Croup score	Humidified air vs control	Not statistically significant: SMD: -0.14, 95%CI [-0.75; 0.47] (p=0.65)	3, 67 vs 68 §	Moore, 2006
Croup score (changes from baseline)	Blow-by-humidity vs low humidity	After 30 minutes: Not statistically significant: MD: 0.03, 95%CI [-0.72; 0.66] (p>0.05) After 60 minutes: Not statistically significant: MD: 0.05, 95%CI [-0.63; 0.74] (p>0.05)	1, 48 vs 46	Scolnik, 2006
	High humidity vs blow-by-humidity	After 30 minutes: Not statistically significant: MD: 0.19, 95%CI [-0.87; 0.49] (p>0.05) After 60 minutes: Not statistically significant: MD: 0.14, 95%CI [-0.54; 0.83] (p>0.05)	1, 46 vs 48	
Hospital admission	Humidified air vs no treatment	Not statistically significant: 6/59 vs 2/60 Peto OR: 3.09, 95%CI [0.71; 13.47] (p=0.13)	2, 59 vs 60 §	Moore, 2006
Oxygen saturation		Not statistically significant: SMD: 0.41, 95%CI [-0.26; 1.09] (p=0.23)	3, 67 vs 68 §	

Mean ± SD (unless otherwise indicated)

* Calculations done by the reviewer(s) using Review Manager software

¥ Imprecision (large variability of results)

§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Moore, 2006	Unclear	Unclear	No	No	
Scolnik, 2006	No, computer generated random block allocation sequence + opaque sealed envelope	No, measurements were blinded	No	No	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence' and systematic review Moore 2006
Imprecision	-1	Limited sample sizes/lack of data/large variability of the results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is limited evidence from 1 experimental studies and 1 systematic review, neither in favour of the intervention nor the control. A statistically significant decrease of heart rate, respiratory rate, croup score, hospital admission or an increase of oxygen saturation, using humidified air compared to no treatment, could not be demonstrated (Moore 2006, Scolnik 2006). Evidence is of low and results of these studies are imprecise due to limited sample size and/or large variability of results.
Reference(s)	**Articles** Scolnik D, Coates AL, Stephens D, Da Silva Z, Lavine E, Schuh S. *Controlled delivery of high vs low humidity vs mist therapy for croup in emergency departments. A randomized controlled trial*. JAMA 2006, 295(11):1274-80 **Systematic reviews** Moore M, Little P. *Humidified air inhalation for treating croup*. Cochrane Database of Systematic Reviews 2006, Issue 3. Art. No.: CD002870. Johnson D. *Croup*. BMJ Clinical Evidence 2014; pii:0321

Croup – Fresh air (First Aid)

Question (PICO)	In an individual with croup (P), is the breathing fresh air (I) compared to no intervention (C) effective to change functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh Croup] OR Croup:ti,ab,kw OR laryngotracheitis:ti,ab,kw OR laryngo-tracheitis:ti,ab,kw 2. [mh ^air] OR air:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Croup[Mesh] OR Croup[TIAB] OR laryngotracheitis[TIAB] OR laryngo-tracheitis[TIAB] 2. Air[Mesh:NoExp] OR ((cold[TIAB] OR fresh[TIAB]) AND air[TIAB]) 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Croup/exp OR croup:ab,ti OR laryngotracheitis:ab,ti OR laryngo-tracheitis:ab,ti 2. Air/de OR 'cold air'/exp OR (cold:ab,ti AND air:ab,ti) OR (fresh:ab,ti AND air:ab,ti) 3. 1-2 AND
Search date	04 November 2015

In/Exclusion criteria	**Population**: Include: Children with symptoms of croup **Intervention**: Include: Breathing of cold air. Exclude: humidified air (different PICO). **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Croup – Hot drinks (First Aid)

Question (PICO)	In an individual with croup (P), is the drinking hot drinks (I) compared to no intervention (C) effective to change functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh Croup] OR Croup:ti,ab,kw OR laryngotracheitis:ti,ab,kw OR laryngo-tracheitis:ti,ab,kw 2. drink*:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. Croup[Mesh] OR Croup[TIAB] OR laryngotracheitis[TIAB] OR laryngo-tracheitis[TIAB] 2. drink*[TIAB] 3. 1-2 AND

	Embase (via Embase.com interface) using the following search strategy: 1. Croup/exp OR croup:ab,ti OR laryngotracheitis:ab,ti OR laryngo-tracheitis:ab,ti 2. drink*:ab,ti 3. 1-2 AND
Search date	04 November 2015
In/Exclusion criteria	**Population**: Include: Children with symptoms of croup **Intervention**: Include: Drinking hot drinks. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

PREGNANCY AND DELIVERY

Miscarriage – Clinical signs (Diagnostics)

Question (PICO)	Among pregnant women (P), are some symptoms (I) more predictive than others (C) for the diagnosis of a spontaneous abortion (miscarriage) (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. MeSH descriptor: [Abortion, Spontaneous] explode all trees and with qualifier(s): [Diagnosis – DI] OR MeSH descriptor: [Pre-Eclampsia] explode all trees and with qualifier(s): [Diagnosis - DI] OR "spontaneous abortion":ti,ab,kw OR "spontaneous abortions":ti,ab,kw OR "tubal abortion":ti,ab,kw OR "tubal abortions":ti,ab,kw OR "miscarriage":ti,ab,kw OR "miscarriages":ti,ab,kw OR "pre-eclampsia":ti,ab,kw OR "preeclampsia":ti,ab,kw OR "pregnancy toxemia":ti,ab,kw 2. MeSH descriptor: [sensitivity and specificity] explode all trees OR MeSH descriptor: [predictive value of tests] explode all trees OR MeSH descriptor: [reference values] explode all trees OR MeSH descriptor: [roc curve] explode all trees OR 'sensitivity':ti,ab,kw OR 'specificity':ti,ab,kw OR 'false positive':ti,ab,kw OR 'false negative':ti,ab,kw OR 'accuracy':ti,ab,kw OR 'predictive value':ti,ab,kw OR 'reference value':ti,ab,kw OR 'reference standard':ti,ab,kw OR 'roc':ti,ab,kw OR 'likelihood ratio':ti,ab,kw 3. signs:ti,ab,kw OR sign:ti,ab,kw OR symptom*:ti,ab,kw 4. 1-3 AND **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Abortion, spontaneous/diagnosis"[Mesh] OR "pre-eclampsia/diagnosis"[Mesh] OR "spontaneous abortion"[TIAB] OR "spontaneous abortions"[TIAB] OR "tubal abortion"[TIAB] OR "tubal abortions"[TIAB] OR "miscarriage"[TIAB] OR "miscarriages"[TIAB] OR "pre-eclampsia"[TIAB] OR "preeclampsia"[TIAB] OR "pregnancy toxemia"[TIAB] 2. signs[tiab] OR sign[tiab] OR symptom*[tiab] 3. "sensitivity and specificity"[Mesh] OR "sensitivity"[TIAB] OR "specificity"[TIAB] OR "predictive value of tests"[Mesh] OR "false positive"[TIAB] OR "false negative"[TIAB] OR "accuracy"[TIAB] OR "predictive value"[TIAB] OR "reference values"[Mesh] OR "reference value"[TIAB] OR"reference standard"[TIAB] OR "roc curve"[Mesh] OR "roc"[TIAB] OR "likelihood ratio"[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'Spontaneous abortion'/exp OR preeclampsia/exp OR "spontaneous abortion":ab,ti OR "spontaneous abortions":ab,ti OR "tubal abortion":ab,ti OR "tubal abortions":ab,ti OR "miscarriage":ab,ti OR "miscarriages":ab,ti OR "pre-eclampsia":ab,ti OR "preeclampsia":ab,ti OR "pregnancy toxemia":ab,ti 2. 'signs':ab,ti OR 'sign':ab,ti OR symptom*:ab,ti 3. 'sensitivity and specificity'/exp OR 'sensitivity':ab,ti OR 'specificity':ab,ti OR 'false positive':ab,ti OR 'false negative':ab,ti OR 'diagnostic accuracy'/exp OR 'accuracy':ab,ti OR 'predictive value'/exp OR 'predictive value':ab,ti OR 'reference value'/exp OR 'reference value':ab,ti OR 'reference standard':ab,ti OR 'receiving operator characteristic'/exp OR 'receiver operating characteristic':ab,ti OR 'roc':ab,ti OR 'likelihood ratio':ab,ti 4. 1-3 AND
Search date	19 June 2015
In/Exclusion criteria	**Population:** Include: pregnant women

	Intervention: Include: clinical symptoms/signs suggestive for a spontaneous abortion (miscarriage) **Comparison:** Include: a diagnostic reference method for the diagnosis of a spontaneous abortion (miscarriage) Exclude: studies not using a diagnostic reference method. **Outcome:** Include: Patient-important outcomes (i.e. survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects)) or accuracy-related outcomes such as sensitivity, specificity and/or positive/negative likelihood ratio (pLR/nLR). Likelihood ratios were considered as the preferred measure of diagnostic accuracy since they are clinically more meaningful than sensitivities, specificities, or diagnostic odds ratios. They quantify how strongly the likelihood of a disease is changed by the presence (pLR) or absence (nLR) of a symptom or sign. A LR of 1 indicates a test result without any diagnostic value. LRs of 1 to 2 or 0.5 to 1 change the likelihood very little and they are rarely important. LRs ≤0.5 or ≥2 change it at least moderately and can be considered as clinically helpful in the context of medical history taking and physical examination. If no information on likelihood ratios is reported, data of sensitivity and specificity are extracted. **Study design:** Include: a systematic review (of diagnostic accuracy studies) was included if the search strategy and selection criteria are clearly described and if at least MEDLINE and one other relevant database was searched. If no systematic review was published within the last 5 years, individual experimental, observational and/or diagnostic accuracy studies were included. Exclude: case series**,** animal studies, *ex vivo* or *in vitro* studies. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline)

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Pre-eclampsia – Clinical signs (Diagnostics)

Question (PICO)	Among pregnant women (P), are some symptoms (I) more predictive than others (C) for the diagnosis of pre-eclampsia (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. MeSH descriptor: [Abortion, Spontaneous] explode all trees and with qualifier(s): [Diagnosis – DI] OR MeSH descriptor: [Pre-Eclampsia] explode all trees and with qualifier(s): [Diagnosis - DI] OR "spontaneous abortion":ti,ab,kw OR "spontaneous abortions":ti,ab,kw OR "tubal abortion":ti,ab,kw OR "tubal abortions":ti,ab,kw OR "miscarriage":ti,ab,kw OR "miscarriages":ti,ab,kw OR "pre-eclampsia":ti,ab,kw OR "preeclampsia":ti,ab,kw OR "pregnancy toxemia":ti,ab,kw 2. MeSH descriptor: [sensitivity and specificity] explode all trees OR MeSH descriptor: [predictive value of tests] explode all trees OR MeSH descriptor: [reference values] explode all trees OR MeSH descriptor: [roc curve] explode all trees OR 'sensitivity':ti,ab,kw OR 'specificity':ti,ab,kw OR 'false positive':ti,ab,kw OR 'false

	negative':ti,ab,kw OR 'accuracy':ti,ab,kw OR 'predictive value':ti,ab,kw OR 'reference value':ti,ab,kw OR 'reference standard':ti,ab,kw OR 'roc':ti,ab,kw OR 'likelihood ratio':ti,ab,kw 3. signs:ti,ab,kw OR sign:ti,ab,kw OR symptom*:ti,ab,kw 4. 1-3 AND **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Abortion, spontaneous/diagnosis"[Mesh] OR "pre-eclampsia/diagnosis"[Mesh] OR "spontaneous abortion"[TIAB] OR "spontaneous abortions"[TIAB] OR "tubal abortion"[TIAB] OR "tubal abortions"[TIAB] OR "miscarriage"[TIAB] OR "miscarriages"[TIAB] OR "pre-eclampsia"[TIAB] OR "preeclampsia"[TIAB] OR "pregnancy toxemia"[TIAB] 2. signs[tiab] OR sign[tiab] OR symptom*[tiab] 3. "sensitivity and specificity"[Mesh] OR "sensitivity"[TIAB] OR "specificity"[TIAB] OR "predictive value of tests"[Mesh] OR "false positive"[TIAB] OR "false negative"[TIAB] OR "accuracy"[TIAB] OR "predictive value"[TIAB] OR "reference values"[Mesh] OR "reference value"[TIAB] OR"reference standard"[TIAB] OR "roc curve"[Mesh] OR "roc"[TIAB] OR "likelihood ratio"[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'Spontaneous abortion'/exp OR preeclampsia/exp OR "spontaneous abortion":ab,ti OR "spontaneous abortions":ab,ti OR "tubal abortion":ab,ti OR "tubal abortions":ab,ti OR "miscarriage":ab,ti OR "miscarriages":ab,ti OR "pre-eclampsia":ab,ti OR "preeclampsia":ab,ti OR "pregnancy toxemia":ab,ti 2. 'signs':ab,ti OR 'sign':ab,ti OR symptom*:ab,ti 3. 'sensitivity and specificity'/exp OR 'sensitivity':ab,ti OR 'specificity':ab,ti OR 'false positive':ab,ti OR 'false negative':ab,ti OR 'diagnostic accuracy'/exp OR 'accuracy':ab,ti OR 'predictive value'/exp OR 'predictive value':ab,ti OR 'reference value'/exp OR 'reference value':ab,ti OR 'reference standard':ab,ti OR 'receiving operator characteristic'/exp OR 'receiver operating characteristic':ab,ti OR 'roc':ab,ti OR 'likelihood ratio':ab,ti 4. 1-3 AND
Search date	19 June 2015
In/Exclusion criteria	**Population:** Include: pregnant women **Intervention:** Include: clinical symptoms/signs suggestive for pre-eclampsia **Comparison:** Include: a diagnostic reference method for the diagnosis of pre-eclampsia Exclude: studies not using a diagnostic reference method. **Outcome:** Include: Patient-important outcomes (i.e. survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects)) or accuracy-related outcomes such as sensitivity, specificity and/or positive/negative likelihood ratio (pLR/nLR). Likelihood ratios were considered as the preferred measure of diagnostic accuracy since they are clinically more meaningful than sensitivities, specificities, or diagnostic odds ratios. They quantify how strongly the likelihood of a disease is changed by the presence (pLR) or absence (nLR) of a symptom or sign. A LR of 1 indicates a test result without any diagnostic value. LRs of 1 to 2 or 0.5 to 1 change the likelihood very little and they are rarely important. LRs ≤0.5 or ≥2 change it at least moderately and can be considered as clinically helpful in the context of medical history taking and physical examination. If no information on likelihood ratios is reported, data of sensitivity and specificity are extracted. **Study design:** Include: a systematic review (of diagnostic accuracy studies) was included if the search strategy and selection criteria are clearly described and if at least MEDLINE and one other relevant database was searched. If no systematic review was published within the last 5 years, individual experimental, observational and/or diagnostic accuracy studies were included. Exclude: case series**,** animal studies, *ex vivo* or *in vitro* studies.

	Language: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline)

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Toxoplasmosis – Baking/steaming/cooking vegetables/meat/fish (Prevention)

Question (PICO)	In humans (P), is baking/steaming/cooking vegetables/meat/fish (I) compared to not baking/steaming/cooking vegetables/meat/fish (C) effective to prevent toxoplasmosis (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh toxoplasmosis] OR [mh listeriosis] OR toxoplasm*:ti,ab,kw OR listeria:ti,ab,kw OR listeriosis:ti,ab,kw 2. Bake:ti,ab,kw OR Baking:ti,ab,kw OR Cook:ti,ab,kw OR Cooking:ti,ab,kw OR Cook:ti,ab,kw OR Cooking:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) using the following search strategy: 1. Toxoplasmosis[Mesh] OR Listeriosis[Mesh] OR Toxoplasm*[TIAB] OR Listeria[TIAB] OR Listeriosis[TIAB] 2. Bake[TIAB] OR Baking[TIAB] OR Cook[TIAB] OR Cooking[TIAB] OR Cook[TIAB] OR Cooking[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Toxoplasmosis/exp OR Listeriosis/exp OR Toxoplasm*:ab,ti OR Listeria:ab,ti OR Listeriosis:ab,ti 2. Bake:ab,ti OR Baking:ab,ti OR Cook:ab,ti OR Cooking:ab,ti OR Cook:ab,ti OR Cooking:ab,ti 3. 1-2 AND
Search date	19 June 2015
In/Exclusion criteria	**Population:** Include: healthy volunteers or people with toxoplasmosis of all ages. **Intervention:** Include: Baking/steaming/cooking vegetables/meat/fish. **Comparison:** Include: No baking/steaming/cooking vegetables/meat/fish. Exclude: studies that only compare different methods of baking/steaming/cooking (different temperatures, different timing, etc.) without a comparison with a baseline measurement (uncooked/unbaked/unsteamed meat/vegetables/fish). **Outcome:** Include: Direct health-related outcomes (e.g. morbidity) or indirect outcomes such as reduction in presence of pathogens, etc. **Study design:** Include: a systematic review was included if the search strategy and selection criteria are clearly described and if at least MEDLINE and one other relevant

	database was searched. If no systematic review was published within the last 5 years, individual experimental and/or observational studies were included. Exclude: case series**,** animal studies, *ex vivo* or *in vitro* studies. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline)

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Listeriosis – Baking/steaming/cooking vegetables/meat/fish (Prevention)

Question (PICO)	In humans (P), is baking/steaming/cooking vegetables/meat/fish (I) compared to not baking/steaming/cooking vegetables/meat/fish (C) effective to prevent listeriosis (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh toxoplasmosis] OR [mh listeriosis] OR toxoplasm*:ti,ab,kw OR listeria:ti,ab,kw OR listeriosis:ti,ab,kw 2. Bake:ti,ab,kw OR Baking:ti,ab,kw OR Cook:ti,ab,kw OR Cooking:ti,ab,kw OR Cook:ti,ab,kw OR Cooking:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) using the following search strategy: 1. Toxoplasmosis[Mesh] OR Listeriosis[Mesh] OR Toxoplasm*[TIAB] OR Listeria[TIAB] OR Listeriosis[TIAB] 2. Bake[TIAB] OR Baking[TIAB] OR Cook[TIAB] OR Cooking[TIAB] OR Cook[TIAB] OR Cooking[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Toxoplasmosis/exp OR Listeriosis/exp OR Toxoplasm*:ab,ti OR Listeria:ab,ti OR Listeriosis:ab,ti 2. Bake:ab,ti OR Baking:ab,ti OR Cook:ab,ti OR Cooking:ab,ti OR Cook:ab,ti OR Cooking:ab,ti 3. 1-2 AND
Search date	19 June 2015
In/Exclusion criteria	**Population:** Include: healthy volunteers or people with listeriosis of all ages. **Intervention:** Include: Baking/steaming/cooking vegetables/meat/fish **Comparison:** Include: No baking/steaming/cooking vegetables/meat/fish. Exclude: studies that only compare different methods of baking/steaming/cooking (different temperatures, different timing, etc.) without a comparison with a baseline measurement (uncooked/unbaked/unsteamed meat/vegetables/fish). **Outcome:** Include: Direct health-related outcomes (e.g. morbidity) or indirect outcomes such as reduction in presence of pathogens, etc. **Study design:** Include: a systematic review was included if the search strategy and selection criteria are clearly described and if at least MEDLINE and one other relevant

	database was searched. If no systematic review was published within the last 5 years, individual experimental and/or observational studies were included. Exclude: case series**,** animal studies, *ex vivo* or *in vitro* studies. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline)

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Pregnancy and delivery – Body position (First Aid)

Question (PICO)	In women during the labour of an emergency delivery (P), is a specific position (I) effective compared to another position (C) to change maternal/foetal health-related outcomes (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh meta-analysis] OR meta analys*:ti,ab,kw OR meta-analys*:ti,ab,kw OR 'cochrane':ti,ab,kw OR 'embase':ti,ab,kw OR 'pubmed':ti,ab,kw OR 'medline':ti,ab,kw OR 'reference list':ti,ab,kw OR 'reference lists':ti,ab,kw OR 'bibliography':ti,ab,kw OR 'bibliographies':ti,ab,kw OR 'hand-search':ti,ab,kw OR 'manual search':ti,ab,kw OR 'selection criteria':ti,ab,kw OR 'relevant journals':ti,ab,kw 2. [mh Labor, Obstetric/adverse effects] OR [mh Labor, Obstetric/mortality] OR [mh Labor, Obstetric/physiology] OR [mh Labor, Obstetric/physiopathology] OR [mh Labor, Obstetric/prevention and control] OR [mh Labor, Obstetric/therapeutic use] OR [mh Labor, Obstetric/therapy] OR labor:ti,ab,kw OR [mh Parturition/adverse effects] OR [mh Parturition/injuries] OR [mh Parturition/mortality] OR [mh Parturition/physiology] OR [mh Parturition/psychology] OR [mh Parturition/rehabilitation] OR [mh Parturition/therapeutic use] OR [mh Parturition/therapy] OR parturition:ti,ab,kw 3. [mh posture] OR 'posture':ti,ab,kw OR 'postures':ti,ab,kw OR position:ti,ab,kw 4. 1-3 AND **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Guideline "[Publication Type] OR "Practice Guidelines as Topic"[Mesh] OR "Practice Guideline "[Publication Type] OR practice guideline*[TIAB] OR Meta-Analysis as Topic[Mesh] OR meta analy*[TIAB] OR metaanaly*[TIAB] OR Meta-Analysis[Publication Type] OR systematic review*[TIAB] OR systematic overview*[TIAB] OR Review Literature as Topic[Mesh] OR cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB] OR reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB] OR selection criteria[TIAB] OR data extraction[TIAB]

	2. "Labor, Obstetric/adverse effects"[Mesh] OR "Labor, Obstetric/mortality"[Mesh] OR "Labor, Obstetric/physiology"[Mesh] OR "Labor, Obstetric/physiopathology"[Mesh] OR "Labor, Obstetric/prevention and control"[Mesh] OR "Labor, Obstetric/therapeutic use"[Mesh] OR "Labor, Obstetric/therapy"[Mesh] OR "labor"[TIAB]) OR "Parturition/adverse effects"[Mesh] OR "Parturition/injuries"[Mesh] OR "Parturition/mortality"[Mesh] OR "Parturition/physiology"[Mesh] OR "Parturition/psychology"[Mesh] OR "Parturition/rehabilitation"[Mesh] OR "Parturition/therapeutic use"[Mesh] OR "Parturition/therapy"[Mesh] OR parturition[TIAB] 3. Posture[Mesh] OR postures[TIAB] OR posture[TIAB] OR position[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti 2. 'labor'/exp OR 'birth'/exp OR 'labor':ab,ti OR 'birth':ab,ti 3. 'body posture'/exp OR posture:ab,ti OR postures:ab,ti OR position:ab,ti 4. 1-3 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	07 July 2015
In/Exclusion criteria	**Population:** Include: women in labour. Exclude: women with epidural analgesia **Intervention:** Include: any body position that can be provided by lay people. Exclude: any body position that can not be provided by lay people (e.g. Trendelenburg position, lithotomy, use of birth stool, birth cushion or birth chair). **Comparison:** Include: studies that compare different body positions **Outcome:** Include: Maternal outcomes: duration of first/second stage of labour, mode of birth (spontaneous vaginal, operative vaginal or caesarean), maternal satisfaction with positioning and with childbirth experience, pain, augmentation of labour, artificial rupture of membranes, use of analgesics, hypotension requiring intervention, estimated blood loss > 500 mL, perineal trauma. Foetal/neonatal outcomes: foetal distress requiring immediate birth, use of neonatal mechanical ventilation, Apgar scores <3/<7 at 5 minutes following birth, <4 at birth, perinatal death. **Study design:** Include: a systematic review was included if the search strategy and selection criteria are clearly described and if at least MEDLINE and one other relevant database was searched. If no systematic review was published within the last 5 years, individual experimental and/or observational studies were included. Exclude: case series**,** animal studies, *ex vivo* or *in vitro* studies. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline)

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Gupta, 2012, United Kingdom	Cochrane systematic review	22 randomized controlled trials including 7280 pregnant women during the second stage of labour	Intervention: the use of any upright or lateral position Control: supine or lithotomy positions	
Lawrence, 2013, Australia	Cochrane systematic review	25 randomized controlled trials including 5218	Intervention: upright (sitting, standing, walking, kneeling, squatting, hands and knees)	

		pregnant women during the first stage of labour	Control: recumbent position (semi-recumbent, lateral, supine, dorsal, bed care)	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
FIRST STAGE OF LABOUR **Maternal outcomes**				
Duration of first stage labour (hours)	Upright and ambulant positions versus recumbent positions and bed care	Statistically significant: MD: -1.36, 95%CI [-2.22; -0.51] (p=0.0017) *In favour of upright and ambulant positions*	15, 1243 vs 1260	Lawrence, 2013
Spontaneous vaginal birth		Not statistically significant: 1105/1306 vs 1084/1320 RR: 1.05, 95%CI [0.99; 1.11] (p=0.09)	14, 1306 vs 1320	
Operative vaginal birth		Not statistically significant: 125/1252 vs 135/1267 § RR: 0.91, 95%CI [0.73; 1.14] ¥ (p=0.40)	13, 1252 vs 1267	
Caesarean birth		Statistically significant: 72/1329 vs 106/1353 RR: 0.71, 95%CI [0.54; 0.94] (p=0.018) *In favour of upright and ambulant positions*	14, 1329 vs 1353	
Maternal satisfaction (satisfaction with position reported at 6 cm)		Not statistically significant: 12/54 vs 9/53 § RR: 1.31, 95%CI [0.60; 2.85] ¥ (p=0.50)	1, 54 vs 53	
Maternal satisfaction (preferred upright position)		Not statistically significant: 42/54 vs 33/53 § RR: 1.25, 95%CI [0.97; 1.61] ¥ (p=0.085)	1, 54 vs 53	
Maternal comfort (comfort score)		Not statistically significant: MD: 0.74, 95%CI [-0.27; 1.75] ¥ (p=0.15)	1, 20 vs 20 §	
Maternal pain (complaints of discomfort/labour more uncomfortable		Not statistically significant: 24/172 vs 43/166 § RR: 0.68, 95%CI [0.12; 3.72] ¥ (p=0.65)	3, 172 vs 166	
Maternal pain (requiring analgesia)		Not statistically significant: 609/771 vs 620/765 RR: 0.95, 95%CI [0.84; 1.08] (p=0.45)	4, 771 vs 765	
Maternal pain (Visual Analogue Scale (VAS) score))		Statistically significant: MD: -1.74, 95%CI [-2.51; -0.97] (p=0.00001) *In favour of upright and ambulant positions*	1, 29 vs 31 §	
Maternal pain (VAS score @ 4 cm)		Statistically significant: MD: -2.00, 95%CI [-2.70; -1.30] (p<0.00001)	1, 48 vs 39 §	

		In favour of upright and ambulant positions		
Maternal pain (VAS score @ 8 cm)		Statistically significant: MD: -1.70, 95%CI [-2.20; -1.20] (p<0.00001) *In favour of upright and ambulant positions*		
Maternal pain (Verbal Response Scale (VRS) score @ 4cm)		Statistically significant: MD: -10.40, 95%CI [-13.27; -7.53] (p<0.00001) *In favour of upright and ambulant positions*		
Maternal pain (Verbal Response Scale (VRS) score @ 8cm)		Statistically significant: MD: -7.00, 95%CI [-11.33; -2.67] (p<0.0015) *In favour of upright and ambulant positions*		
Maternal pain (Present Pain Intensity Scale (PPI) @4cm)		Not statistically significant: MD: -1.40, 95%CI [-3.61; 0.81] ¥ (p=0.21)		
Maternal pain (Present Pain Intensity Scale (PPI) @8cm)		Not statistically significant: MD: -0.80, 95%CI [-3.76; 2.16] ¥ (p=0.60)		
Maternal anxiety		Not statistically significant: MD: 8.00, 95%CI [-0.19; 16.19] ¥ (p=0.055)	1, 100 vs 100 §	
Duration of second stage of labour (hours)		Not statistically significant: MD: -3.71, 95%CI [-9.37; 1.94] (p=0.20)	9, 1035 vs 1042	
Augmentation of labour using oxytocin		Not statistically significant: MD: 0.89, 95%CI [0.76; 1.05] (p=0.18)	8, 880 vs 946	
Artificial rupture of membranes		Not statistically significant: 111/132 vs 122/144 § RR: 1.02, 95%CI [0.95; 1.10] (p=0.54)	4, 132 vs 144	
Estimated blood loss >500 mL		Not statistically significant: 2/120 vs 3/120 § RR: 0.71, 95%CI [0.14; 3.55] ¥ (p=0.68)	2, 120 vs 120	
Perineal trauma		Not statistically significant: 236/690 vs 254/684 RR: 0.92, 95%CI [0.82; 1.04] (p=0.20)	3, 690 vs 684	
Duration of first stage labour (hours)	Sitting vs recumbent/supine/ lateral	Statistically significant: MD: -2.39, 95%CI [-4.06; -0.72] (p=0.005) *In favour of sitting*	3, 111 vs 141 §	
Spontaneous vaginal birth		Not statistically significant: 74/81 vs 118/144 § RR: 1.20, 95%CI [0.88; 1.64] ¥ (p=0.25)	2, 81 vs 144	
Operative vaginal birth		Statistically significant: 2/81 vs 16/144 § RR: 0.18, 95%CI [0.04; 0.75] (p=0.018) *In favour of sitting*	2, 81 vs 144	

Caesarean birth		Not statistically significant: 5/81 vs 10/144 § RR: 1.02, 95%CI [0.36; 2.84] ¥ (p=0.98)	2, 81 vs 144	
Duration of first stage labour (hours)	Walking vs recumbent/supine/ lateral	Statistically significant: MD: -3.96, 95%CI [-5.36; -2.57] (p<0.00001) *In favour of walking*	3, 152 vs 150	
Spontaneous vaginal birth		Statistically significant: 133/153 vs 106/153 § RR: 1.26, 95%CI [1.11; 1.42] (p=0.0002) *In favour of walking*	3, 133 vs 106	
Operative vaginal birth		Statistically significant: 15/153 vs 30/153 § RR: 0.50, 95%CI [0.28; 0.89] (p=0.017) *In favour of walking*	3, 153 vs 153	
Caesarean birth		Statistically significant: 5/153 vs 17/153 § RR: 0.31, 95%CI [0.12; 0.79] (p=0.014) *In favour of walking*	3, 153 vs 153	
Duration of first stage labour (hours)	Sitting, standing, squatting, kneeling or walking vs recumbent/supine/ lateral	Not statistically significant: MD: -1.02, 95%CI [-3.36; 1.33] (p=0.40)	2, 153 vs 158	
Spontaneous vaginal birth		Not statistically significant: 86/119 vs 84/116 § RR: 1.00, 95%CI [0.85; 1.17] (p=0.98)	2, 119 vs 116	
Operative vaginal birth		Not statistically significant: 25/119 vs 26/116 § RR: 0.94, 95%CI [0.58; 1.52] ¥ (p=0.79)	2, 119 vs 116	
Caesarean birth		Not statistically significant: 8/119 vs 6/116 § RR: 1.30, 95%CI [0.46; 3.63] ¥ (p=0.62)	2, 119 vs 116	
Duration of first stage labour (hours)	Sitting versus bed care	Not statistically significant: MD: 0.11, 95%CI [-0.29; 0.51] (p=0.59)	1, 29 vs 31 §	
Caesarean birth		Not statistically significant: 1/31 vs 0/31 § RR: 3.00, 95%CI [0.13; 70.92] ¥ (p=0.50)	1, 31 vs 31 §	
Duration of first stage labour (hours)	Walking versus bed care	Not statistically significant: MD: -0.03, 95%CI [-0.44; 0.38] (p=0.89)	2, 584 vs 586	
Spontaneous vaginal birth		Not statistically significant: 632/720 vs 615/706 RR: 1.01, 95%CI [0.93; 1.11] (p=0.77)	3, 720 vs 706	
Operative vaginal birth		Not statistically significant: 58/720 vs 49/706 § RR: 1.19, 95%CI [0.84; 1.68] ¥ (p=0.34)	4, 720 vs 706	
Caesarean birth		Not statistically significant:	4, 720 vs 706	

		30/720 vs 42/706 § RR: 0.70, 95%CI [0.45; 1.09] ¥ (p=0.12)		
Duration of first stage labour (hours)	Sitting, standing, squatting, kneeling or walking vs bed care	Not statistically significant: MD: -0.52, 95%CI [-1.49; 0.45] (p=0.29)	4, 214 vs 210	
Spontaneous vaginal birth		Not statistically significant: 180/233 vs 174/221 RR: 1.00, 95%CI [0.92; 1.08] (p=0.97)	4, 233 vs 221	
Operative vaginal birth		Not statistically significant: 25/179 vs 21/168 § RR: 1.19, 95%CI [0.84; 1.68] (p=0.34)	3, 179 vs 168	
Caesarean birth		Not statistically significant: 23/225 vs 31/223 § RR: 0.74, 95%CI [0.46; 1.21] ¥ (p=0.23)	3, 225 vs 223	
FIRST STAGE OF LABOUR **Foetal/neonatal outcomes**				
Foetal distress (requiring immediate delivery)	Upright and ambulant positions versus recumbent positions and bed care	Not statistically significant: 12/848 vs 20/909 § RR: 0.69, 95%CI [0.35; 1.33] ¥ (p=0.26)	6, 848 vs 909	Lawrence, 2013
Use of neonatal mechanical ventilation		Not statistically significant: 3/556 vs 4/551 § RR: 0.77, 95%CI [0.19; 3.10] ¥ (p=0.72)	2, 556 vs 551	
Apgar score <4 at birth		Not statistically significant: 0/20 vs 2/20 RR: 0.20, 95%CI [0.01; 3.92] (p=0.29)	1, 20 vs 20	
Apgar score <7 at 1 min		Not statistically significant: 31/349 vs 38/357 § RR: 0.84, 95%CI [0.54; 1.31] ¥ (p=0.45)	6, 349 vs 357	
Apgar score <7 at 5 mins		Not statistically significant: 2/229 vs 0/237 § RR: 3.27, 95%CI [0.34; 31.05] ¥ (p=0.30)	4, 229 vs 237	
Apgar score <8 at 5 mins		Not statistically significant: 0/48 vs 3/39 § RR: 0.12, 95%CI [0.01; 2.19] ¥ (p=0.15)	1, 48 vs 39	
Perinatal mortality		Not statistically significant: 1/784 vs 2/780 § RR: 0.50, 95%CI [0.05; 5.37] ¥ (p=0.56)	5, 784 vs 780	
SECOND STAGE OF LABOUR **Maternal outcomes**				
Any analgesia/ anaesthesia during second stage of labour	Any upright versus supine position	Not statistically significant: 1034/1823 vs 1020/1770 RR: 0.97, 95%CI [0.92; 1.02] (p=0.24)	7, 1823 vs 1770	Gupta, 2012
Duration of second stage of labour		Not statistically significant: MD: -3.71, 95%CI [-8.78; 1.37] (p=0.15)	10, 1773 vs 1712	

Assisted delivery		Statistically significant: 297/2995 vs 379/3029 RR: 0.78, 95%CI [0.68; 0.90] (p=0.00055) *In favour of upright position*	19, 2995 vs 3029	
Caesarean section		Not statistically significant: 27/2406 vs 28/2418 § RR: 0.97, 95%CI [0.59; 1.59] ¥ (p=0.90)	13, 2406 vs 2418	
Second degree perineal tears		Statistically significant: 477/2658 vs 376/2709 RR: 1.35, 95%CI [1.20; 1.51] (p<0.00001) *In favour of upright position*	14, 2658 vs 2709	
Episiotomy		Statistically significant: 797/2268 vs 977/2273 RR: 0.79, 95%CI [0.70; 0.90] (p=0.00035) *In favour of upright position*	12, 2268 vs 2273	
Third/fourth degree tears		Not statistically significant: 5/824 vs 10/861 § RR: 0.58, 95%CI [0.22; 1.52] ¥ (p=0.27)	5, 824 vs 861	
Blood loss >500mL		Statistically significant: 186/2562 vs 114/2596 RR: 1.65, 95%CI [1.32; 2.06] (p=0.000013) *In favour of upright position*	13, 2562 vs 2596	
Need for blood transfusion		Not statistically significant: 14/891 vs 8/856 § RR: 1.66, 95%CI [0.70; 3.94] ¥ (p=0.25)	2, 891 vs 856	
SECOND STAGE OF LABOUR **Foetal/neonatal outcomes**				
Abnormal foetal heart rate	Any upright versus supine position	Statistically significant: 10/307 vs 22/310 § RR: 0.46, 95%CI [0.22; 0.93] (p=0.030) *In favour of upright position*	2, 307 vs 310	Gupta, 2012
Perinatal mortality		Not statistically significant: 3/418 vs 4/409 § RR: 0.75, 95%CI [0.17; 3.31] ¥ (p=0.70)	2, 418 vs 409	

Mean ± SD (unless otherwise indicated)

¥ Imprecision (large variability of results)

§ Imprecision (limited sample size or low number of events)

Level of evidence

First stage of labour ***Maternal outcomes***	**Initial grading High [A]**	Downgrading due to
Limitations of study design	-1	See systematic review of Lawrence 2013
Imprecision	-1	Limited sample sizes/low number of events and large variability of the results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

First stage of labour *Fetal/neonatal outcomes*	**Initial grading High [A]**	Downgrading due to
Limitations of study design	-1	See systematic review of Lawrence 2013
Imprecision	-1	Low number of events and large variability in results
Inconsistency	0	
Indirectness	0	
Publication bias	0	[Conflict of interest]
QUALITY (GRADE)	**Final grading Low [C]**	

Second stage of labour *Maternal outcomes*	**Initial grading High [A]**	Downgrading due to
Limitations of study design	-1	See systematic review of Gupta 2012
Imprecision	0	
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Moderate [B]**	

Second stage of labour *Foetal/neonatal outcomes*	**Initial grading High [A]**	Downgrading due to
Limitations of study design	-1	See systematic review of Gupta 2012
Imprecision	-1	Low number of events
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	FIRST STAGE OF LABOUR (maternal outcomes) **Upright and ambulant positions versus recumbent positions and bed care** There is limited evidence in favour of upright and ambulant positions. In making this evidence conclusion, we place a higher value on statistically significant outcomes over non-statistically significant outcomes. It was shown that upright and ambulant positions resulted in a statistically significant decreased duration of first stage labour, a decreased risk of caesarean birth and a decreased risk of maternal, compared to recumbent positions and bed care (Lawrence 2013). However, a statistically significant difference in spontaneous vaginal birth, operative vaginal birth, maternal satisfaction, maternal comfort, maternal anxiety, duration of second stage of labour, augmentation of labour using oxytocin, artificial rupture of membranes, estimated blood loss >500 mL, perineal trauma, using upright and ambulant positions compared to recumbent positions and bed care, could not be demonstrated (Lawrence 2013). Evidence is of low quality and results cannot be considered precise due to limited sample size and large variability of results. **Sitting vs recumbent/supine/lateral** There is limited evidence in favour of sitting. In making this evidence conclusion, we place a higher value on statistically significant outcomes over non-statistically significant outcomes. It was shown that sitting resulted in a statistically significant decreased duration of first stage labour and a decreased risk of operative vaginal birth, compared to recumbent/supine/lateral positions (Lawrence 2013). However, a statistically significant difference in spontaneous vaginal birth and caesarean birth, using sitting position compared to recumbent/supine/lateral positions, could not be demonstrated (Lawrence 2013). Evidence is of low quality and results cannot be considered precise due to the large variability of results.

	Walking vs recumbent/supine/lateral There is limited evidence in favour of walking. It was shown that walking resulted in a statistically significant increase in spontaneous vaginal birth, a decreased duration of first stage labour and a decreased risk of operative vaginal and caesarean birth, compared to recumbent/supine/lateral positions (Lawrence 2013). Evidence is of moderate quality. **Sitting, standing, squatting, kneeling or walking vs recumbent/supine/lateral** There is limited evidence neither in favour of sitting, standing, squatting, kneeling or walking nor the recumbent/supine/lateral position. A statistically significant difference in duration of first labour, spontaneous vaginal birth, operative birth and caesarean birth, using sitting, standing, squatting, kneeling or walking compared to recumbent/supine/lateral position, could not be demonstrated (Lawrence 2013). Evidence is of low quality and results are imprecise due to large variability of results. **Sitting versus bed care** There is limited evidence neither in favour of sitting nor bed care. A statistically significant difference in duration of first labour, and caesarean birth using sitting compared to bed care, could not be demonstrated (Lawrence 2013). Evidence is of low quality and results are imprecise due to limited sample size and large variability of results. **Walking versus bed care** There is limited evidence neither in favour of walking nor the bed care. A statistically significant difference in duration of first labour, spontaneous vaginal birth, operative birth and caesarean birth, using walking compared to bed care, could not be demonstrated (Lawrence 2013). Evidence is of low quality and results are imprecise due to large variability of results. **Sitting, standing, squatting, kneeling or walking vs bed care** There is limited evidence neither in favour of sitting, standing, squatting, kneeling or walking nor bed care. A statistically significant difference in duration of first labour, spontaneous vaginal birth, operative birth and caesarean birth, using walking compared to bed care, could not be demonstrated (Lawrence 2013). Evidence is of low quality and results are imprecise due to low number of events and large variability of results. <u>FIRST STAGE OF LABOUR (foetal/neonatal outcomes)</u> **Upright and ambulant positions versus recumbent positions and bed care** There is limited evidence neither in favour of upright and ambulant positions nor recumbent positions and bed care. A statistically significant difference in foetal distress, use of neonatal mechanical ventilation, Apgar scores and perinatal mortality, using upright and ambulant positions compared to recumbent positions and bed care, could not be demonstrated (Lawrence 2013). Evidence is of low quality and results are imprecise due to low number of events and large variability of results. <u>SECOND STAGE OF LABOUR (maternal outcomes)</u> **Any upright versus supine position** There is limited evidence in favour of any upright position. In making this evidence conclusion, we place a higher value on statistically significant outcomes over non-statistically significant outcomes. It was shown that any upright position resulted in a statistically significant decreased risk of assisted delivery, second degree of perineal tears and episiotomy and an increased

	risk of blood loss >500mL, compared to the supine position (Gupta 2012). However, a statistically significant difference in any analgesia/anaesthesia during second stage of labour, duration of second stage of labour, caesarean section, third/fourth degree tears and the need for blood transfusion, using any upright position compared to the supine position, could not be demonstrated (Gupta 2012). Evidence is of moderate quality. SECOND STAGE OF LABOUR (foetal/neonatal outcomes) **Any upright versus supine position** There is limited evidence in favour of any upright position. In making this evidence conclusion, we place a higher value on statistically significant outcomes over non-statistically significant outcomes. It was shown that any upright position resulted in a statistically significant decreased risk of abnormal foetal heart rate, compared to the supine position (Gupta 2012). However, a statistically significant difference in perinatal mortality, using any upright position compared to the supine position, could not be demonstrated (Gupta 2012). Evidence is of low quality and results cannot be considered precise due to the low number of events.
Reference(s)	**Systematic reviews** Gupta JK, Hofmeyr GJ, Shehmar M. *Position in the second stage of labour for women without epidural anaesthesia.* Cochrane Database Syst Rev. 2012, 5:CD002006. Lawrence A, Lewis L, Hofmeyr GJ, Styles C. *Maternal positions and mobility during first stage labour*. Cochrane Database Syst Rev. 2013, 10:CD003934.

Pregnancy and delivery – Early skin-to-skin contact by mothers (First Aid)

Question (PICO)	In new-born babies (P), is early skin-to-skin contact by mothers (I) compared to no skin-to-skin contact (C) effective for health-related outcomes (O)?
Search Strategy	The starting point for this PICO was the NICE guideline 2007 entitled 'Intrapartum care'. This guideline includes a Cochrane systematic review of 2003 (Anderson, 2003, USA) which addressed this PICO question and was used as source of individual studies. The updated version of this review, i.e. Moore, 2012, USA, was included to answer this PICO question. Therefore, no search strategies regarding additional experimental studies (i.e. randomized controlled trials) were performed since the Cochrane systematic review will be updated every 5 years. Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	13 July 2015
In/Exclusion criteria	**Population:** Include: Mothers and their healthy full term or late preterm new-born infants (34 to less than 37 completed weeks' gestation) having early skin-to-skin contact starting less than 24 hours after birth, and controls undergoing standard patterns of care. **Intervention:** Include: Early skin-to-skin for term or late preterm infants which can be divided into 'birth skin-to-skin contact', 'very early skin-to-skin contact' and early skin-to-skin contact' (for details: see Moore 2012). In the future these groups may be analyzed separately. However, at present, not enough studies are available for subgroup analysis. **Comparison:** Include: Standard contact which includes a number of diverse conditions, infants held swaddled or dressed in their mothers arms, or infants placed in open cribs or under radiant warmers in the mother's room or elsewhere with no holding allowed. **Outcome:** Include: direct health-related outcomes (breastfeeding/infant/maternal outcomes **Study design:** Include: a systematic review was included if the search strategy and selection criteria are clearly described and if at least MEDLINE and one other relevant database was searched. If no systematic review was published within the last 5 years, individual experimental and/or observational studies were included.

	Exclude: case series**,** animal studies, *ex vivo* or *in vitro* studies. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline)

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Moore, 2012, USA	Cochrane systematic review	34 randomized controlled trials involving 2177 participants (mother-infant dyads)	Intervention: early skin-to-skin for term or late preterm infants which can be divided into 'birth skin-to-skin contact', 'very early skin-to-skin contact' and early skin-to-skin contact' Control: standard contact which includes a number of diverse conditions, infants held swaddled or dressed in their mothers arms, or infants placed in open cribs or under radiant warmers in the mother's room or elsewhere with no holding allowed.	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Breastfeeding outcomes				
Breastfeeding 1 month to 4 months post birth	Skin-to-skin vs standard contact	Statistically significant: 225/353 vs 175/349 RR: 1.27, 95%CI [1.06;1.53] (p=0.0093) *In favour of skin-to-skin contact*	13, 353 vs 349	Moore, 2012
Duration of breastfeeding in days		Not statistically significant: MD: 42.55, 95%CI [-1.69;86.79] (p=0.059) £†	7, 164 vs 160 §	
Success of the first breastfeeding (IBFAT score)		Statistically significant: MD: 1.79, 95%CI [0.24;3.35] (p=0.024) £ *In favour of skin-to-skin contact*	2, 27 vs 27 §	
Exclusive breastfeeding at hospital discharge		Not statistically significant: 17/28 vs 18/29 § RR: 0.99, 95%CI [0.66;1.47] (p=0.94) ¥	2, 28 vs 29	
Breastfeeding status day 28 to 1 month post birth		Not statistically significant: MD: 0.86, 95%CI [-0.73;2.44] (p=0.29) £	3, 121 vs 124 §	
Exclusive breastfeeding up to 3-6 months post birth		Statistically significant: 44/72 vs 24/77 § RR: 1.97, 95%CI [1.37;2.83] (p=0.00026) *In favour of skin-to-skin contact*	3, 72 vs 77	
Breastfeeding 1 year post birth		Not statistically significant: 7/35 vs 0/27 § RR: 6.19, 95%CI [0.82;46.78] (p=0.077) ¥	2, 35 vs 27	
Suckled during the first 2 hours post birth		Not statistically significant: 34/44 vs 32/44 § RR: 1.06, 95%CI [0.83;1.35] (p=0.62) ¥	1, 44 vs 44	

Mean variation in maternal breast temperature 30-120 minutes post birth		Statistically significant: MD: 0.60, 95%CI [0.34;0.86] (p<0.00001) £ *In favour of skin-to-skin contact*	1, 44 vs 88 §	
Breast engorgement (pain, tension, hardness) 3 days post birth		Statistically significant: MD: -0.41, 95%CI [-0.76;-0.06] (p=0.020) £ *In favour of skin-to-skin contact*	2, 65 vs 66 §	
Infant outcomes				
SCRIP score first 6 hours post birth		Statistically significant: MD: 2.88, 95%CI [0.53;5.23] (p=0.016) £ *In favour of skin-to-skin contact*	1, 18 vs 13 §	Moore, 2012
SCRIP score first 6 hours in new-borns below 1800g birth weight		Not statistically significant: MD: 4.92, 95%CI [-1.67;11.51] (p=0.14) £†	1, 9 vs 4 §	
Blood glucose mg/dL and mmol/l at 75-90 minutes post birth		Statistically significant: MD: 10.56, 95%CI [8.40;12.72] (p<0.000001) *In favour of skin-to-skin contact*	2, 47 vs 47 §	
Heart rate 75 minutes to 2 hours post birth		Not statistically significant: MD: -3.05, 95%CI [-7.84;1.75] (p=0.21) £†	3, 91 vs 92 §	
Respiratory rate 75 minutes – 2 hours post birth		Not statistically significant: MD: -3.12, 95%CI [-6.61;0.37] (p=0.080) £†	4, 106 vs 109 §	
Infant did not exceed parameters for stability		Statistically significant: 15/18 vs 1/13 § RR: 10.83, 95%CI [1.63;72.02] (p=0.014) *In favour of skin-to-skin contact*	1, 18 vs 13	
Transferred to the neonatal intensive care unit		Not statistically significant: 2/18 vs 1/13 § RR: 1.44, 95%CI [0.15;14.29] (p=0.75) ¥	1, 18 vs 13	
Infant body weight change (grams) day 14 post birth		Not statistically significant: MD: -8.00, 95%CI [-175.60; 159.61] (p=0.93) £†	2, 21 vs 22 §	
Infant hospital length of stay in hours		Not statistically significant: MD: -95.30, 95%CI [-368.50; 177.89] (p=0.49) £†	2, 21 vs 21 §	
Not crying for >1 minute during 90 minutes		Statistically significant: MD: 12.86, 95%CI [1.91;86.44] (p=0.0086) £ *In favour of skin-to-skin contact*	1, 14 vs 15 §	
Amount of crying in minutes during a 75-minute observation period		Statistically significant: MD: -8.01, 95%CI [-8.98;-7.04] (p<0.00001) £ *In favour of skin-to-skin contact*	1, 22 vs 22 §	
Maternal outcomes				
Maternal pain 4 hours post caesarean birth		Not statistically significant: MD: -1.38, 95%CI [-2.79;0.03] (p=0.054) £†	1, 20 vs 15 §	Moore, 2012
Mother's most certain preference for same		Statistically significant: MD: 2.82, 95%CI [2.08;3.82] (p<0.00001) £	1, 97 vs 102 §	

post delivery care in the future		*In favour of skin-to-skin contact*		
Maternal state anxiety day 3 post birth		Statistically significant: MD: -5.00, 95%CI [-9.00;-1.00] (p=0.014) £ *In favour of skin-to-skin contact*	1, 28 vs 28 §	
Maternal parental confidence at 1 month post birth		Not statistically significant: MD: 5.60, 95%CI [-6.24;17.44] (p=0.35) £†	1, 10 vs 10 §	

£ No raw data available
§ Imprecision (limited sample size or low number of events)
¥ Imprecision (large variability of results)
† Imprecision (lack of data)

Level of evidence

Breastfeeding outcomes	**Initial grading High [A]**	Downgrading due to
Limitations of study design	-1	See systematic review Moore 2012
Imprecision	-1	Limited sample size/low number of events and/or large variability in results and/or lack of data
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Infant outcomes	**Initial grading High [A]**	Downgrading due to
Limitations of study design	-1	See systematic review Moore 2012
Imprecision	-1	Limited sample size/low number of events and/or large variability in results and/or lack of data
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Maternal outcomes	**Initial grading High [A]**	Downgrading due to
Limitations of study design	-1	See systematic review Moore 2012
Imprecision	-1	Limited sample size and lack of data
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	**Breastfeeding outcomes** There is limited evidence in favour of skin-to-skin contact. In making this evidence conclusion, we place a higher value on statistically significant outcomes and clinically relevant outcomes (but not statistically different) over non-statistically significant outcomes. It was shown that skin-to-skin contact resulted in a statistically significant increased number of mothers breastfeeding 1 month to 4 months post birth, an increased success of the first breastfeeding, an increased exclusive breastfeeding up to 3-6 months post birth, an increased mean variation in maternal breast temperature 30-120 minutes post birth and a decreased risk of breast engorgement (pain, tension, hardness) 3 days post birth, compared to standard contact (Moore, 2012). However, a statistically significant difference in 5 other breastfeeding outcomes (see table 'synthesis of findings), could not be demonstrated (Moore 2012).

	Evidence is of low quality and results are imprecise due to the limited sample size/low number of events and large variability in results. **Infant outcomes** There is limited evidence in favour of skin-to-skin contact. In making this evidence conclusion, we place a higher value on statistically significant outcomes and clinically relevant outcomes (but not statistically different) over non-statistically significant outcomes. It was shown that skin-to-skin contact resulted in a statistically significant increased infant stabilization during the transition to extra-uterine life (SCRIP score), increased blood glucose levels and a decreased risk of crying, compared to standard contact (Moore, 2012). However, a statistically significant difference in 6 other infant outcomes (see table 'synthesis of findings), could not be demonstrated (Moore 2012). Evidence is of low quality and results are imprecise due to the limited sample size/low number of events and large variability in results. **Maternal outcomes** There is limited evidence in favour of skin-to-skin contact. In making this evidence conclusion, we place a higher value on statistically significant outcomes and clinically relevant outcomes (but not statistically different) over non-statistically significant outcomes. It was shown that skin-to-skin contact resulted in a statistically significant increased maternal sensitivity to her infant's cues and a decreased level of anxiety, compared to standard contact (Moore, 2012). However, a statistically significant difference in 2 other maternal outcomes (see table 'synthesis of findings), could not be demonstrated (Moore 2012). Evidence is of low quality and results are imprecise due to the limited sample size/low number of events and large variability in results.
Reference(s)	**Systematic reviews** Moore ER, Anderson GC, Bergman N, Dowswell T. Early skin-to-skin contact for mothers and their healthy newborn infants. Cochrane Database Syst Rev 2012, 5:CD003519.

Pregnancy and delivery – Cutting/clamping umbilical cord (technique) (First Aid)

Question (PICO)	In new-born babies (P), which technique to cut/clamp the umbilical cord is (I) effective to direct health-related maternal/neonatal outcomes (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh Labor, Obstetric/adverse effects] OR labor:ti,ab,kw OR labour:ti,ab,kw OR [mh Parturition] OR parturition:ti,ab,kw 2. 'cut':ti,ab,kw OR 'cutting':ti,ab,kw OR clamp*:ti,ab,kw 3. [mh umbilical Cord] OR 'umbilical cord':ti,ab,kw OR 'umbilical cords':ti,ab,kw 4. 1-3 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy (limits: humans): 1. "Labor, Obstetric/adverse effects"[Mesh] OR "Labor, Obstetric/mortality"[Mesh] OR "Labor, Obstetric/physiology"[Mesh] OR "Labor, Obstetric/physiopathology"[Mesh] OR "Labor, Obstetric/prevention and control"[Mesh] OR "Labor, Obstetric/therapeutic use"[Mesh] OR "Labor, Obstetric/therapy"[Mesh] OR "labor"[TIAB] OR "labour"[TIAB] OR "Parturition/adverse effects"[Mesh] OR "Parturition/injuries"[Mesh] OR "Parturition/mortality"[Mesh] OR "Parturition/physiology"[Mesh] OR

	"Parturition/psychology"[Mesh] OR "Parturition/rehabilitation"[Mesh] OR "Parturition/therapeutic use"[Mesh] OR "Parturition/therapy"[Mesh] OR parturition[TIAB] 2. "cut"[TIAB] OR "cutting"[TIAB] OR clamp*[TIAB] 3. "umbilical Cord"[Mesh] OR "umbilical cord"[TIAB] OR "umbilical cords"[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy (limits: humans): 1. 'labor'/exp OR 'birth'/exp OR 'labor':ab,ti OR 'labour':ab,ti OR 'birth':ab,ti 2. 'cut':ab,ti OR 'cutting':ab,ti OR clamp*:ab,ti 3. 'umbilical cord'/exp OR 'umbilical cord':ab,ti OR 'umbilical cords':ab,ti 4. 1-3 AND
Search date	13 July 2015
In/Exclusion criteria	**Population:** Included: women who have given birth to a (pre-)term infant **Intervention:** Include: umbilical cord clamping/cutting using a specific technique **Comparison:** Include: umbilical cord clamping/cutting using another technique **Outcome:** Include: direct health-related outcomes related to the mother (maternal outcomes) or the neonate (neonatal outcomes). **Study design:** Include: a systematic review was included if the search strategy and selection criteria are clearly described and if at least MEDLINE and one other relevant database was searched. If no systematic review was published within the last 5 years, individual experimental and/or observational studies were included. Exclude: case series**,** animal studies, *ex vivo* or *in vitro* studies. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline)

Characteristics of included studies
Not applicable

Synthesis of findings
No relevant studies were identified using the above search strategy and criteria.

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Pregnancy and delivery – Timing of umbilical cord clamping (First Aid)

Question (PICO)	In neonates (P), is early umbilical cord clamping (I) compared to late or delayed umbilical cord clamping (C) effective to improve maternal and neonatal outcomes (O)?
Search Strategy	The starting point for this PICO was the NICE guideline 2014 entitled 'Intrapartum care: care of healthy women and their babies during childbirth'. This guideline includes a Cochrane systematic review of 2013 (McDonald, 2013, Australia) which addressed this PICO question and was used as source of individual studies. Therefore, no search strategies regarding additional experimental studies (i.e. randomized controlled trials) were performed since the Cochrane systematic review will be updated every 5 years. Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	10 July 2015
In/Exclusion criteria	**Population:** Included: women who 1) have given birth to a term infant (equal to or greater than 37 completed weeks' gestation); and 2) have been involved in a birth where clamping of the umbilical cord is applied (including caesarean section).

	Excluded: 1) women who have given birth to a pre-term infant (less than 37 weeks' gestation), 2) breech presentation, 3) multiple pregnancies. **Intervention:** Include: early cord clamping, defined as application of a clamp to the umbilical cord within 60 seconds of the birth of the infant **Comparison:** Include: later (delayed) cord clamping, defined as application of a clamp to the umbilical cord greater than one minute after birth or when cord pulsation has ceased **Outcome:** Include: direct health-related outcomes related to the mother (maternal outcomes) or the neonate (neonatal outcomes), outcomes measured with uterotonic at or after clamping. Excluded: direct health-related maternal/neonatal outcomes measured with uterotonic before clamping or studies where timing of uterotonic was not specified. **Study design:** Include: a systematic review was included if the search strategy and selection criteria are clearly described and if at least MEDLINE and one other relevant database was searched. If no systematic review was published within the last 5 years, individual experimental and/or observational studies were included. Exclude: case series**,** animal studies, *ex vivo* or *in vitro* studies. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline)

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
McDonald, 2013, Australia	Cochrane systematic review	15 randomized controlled trials involving 3911 women and infant pairs. Women were included if they 1) have given birth to a term infant (equal to or greater than 37 completed weeks' gestation); and 2) have been involved in a birth where clamping of the umbilical cord is applied (including caesarean section).	Intervention: early cord clamping, defined as application of a clamp to the umbilical cord within 60 seconds of the birth of the infant Control: later (delayed) cord clamping, defined as application of a clamp to the umbilical cord greater than one minute after birth or when cord pulsation has ceased	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Severe post-partum haematoma (blood loss 1000 mL or more)	Early vs late cord clamping	Not statistically significant: 20/478 vs 19/478 § RR: 1.06, 95%CI [0.57;1.95] (p=0.86) ¥	3, 478 vs 478	McDonald, 2013
Neonatal death		Not statistically significant: 1/142 vs 3/239 § RR: 0.37, 95%CI [0.04;3.41] (p=0.38) ¥	1, 142 vs 239	
Post-partum haemorrhage (blood loss 500 mL or more)		Not statistically significant: 77/478 vs 63/478 § RR: 1.22, 95%CI [0.90;1.65] (p=0.20) ¥	3, 478 vs 478	
Mean blood loss (mL)		Not statistically significant: MD: 0.70 95%CI [-31.06;32.46] (p=0.97)	2, 433 vs 432	

Maternal haemoglobin (g/dL) 24 to 72 hours postpartum		Not statistically significant: MD: -0.10 95%CI [-0.42;0.22] (p=0.54)	1, 244 vs 239	
Need for blood transfusion		Not statistically significant: 7/433 vs 8/432 § RR: 0.89, 95%CI [0.34;2.35] (p=0.82) ¥	2, 433 vs 432	
Need for manual removal of placenta.		Not statistically significant: 2/244vs 4/239 § RR: 0.49, 95%CI [0.09;2.65] (p=0.41) ¥	1, 244 vs 239	
Length of third stage > 30 mins		Not statistically significant: 11/433 vs 11/432 § RR: 1.01, 95%CI [0.44;2.29] (p=0.98) ¥	2, 433 vs 432	
Length of third stage > 60 mins		Not statistically significant: 6/433 vs 4/432 § RR: 1.68, 95%CI [0.09;31.66] (p=0.73) ¥		
Need for therapeutic uterotonics		Not statistically significant: 48/244 vs 58/239 § RR: 0.81, 95%CI [0.58;1.14] (p=0.22) ¥	1, 244 vs 239	
Apgar score < 7 at 5 mins		Not statistically significant: 8/272 vs 6/268 § RR: 1.96, 95%CI [0.60;6.42] (p=0.27) ¥	2, 272 vs 268	
Any admission to SCN or NICU		Not statistically significant: 14/433 vs 19/432 § RR: 0.74, 95%CI [0.37;1.46] (p=0.38) ¥	2, 433 vs 432	
Respiratory distress		Not statistically significant: 29/466 vs 28/369 § RR: 0.70, 95%CI [0.22;2.19] (p=0.53) ¥	3, 466 vs 369	
Jaundice requiring phototherapy		Not statistically significant: 15/549 vs 24/563 § RR: 0.64, 95%CI [0.35;1.18] (p=0.16) ¥	5, 549 vs 563	
Clinical jaundice		Not statistically significant: 33/286 vs 41/290 § RR: 0.87, 95%CI [0.57;1.31] (p=0.49) ¥	2, 286 vs 290	
Polycythaemia		Not statistically significant: 1/280 vs 4/297 § RR: 0.38, 95%CI [0.06;2.48] (p=0.31) ¥	3, 280 vs 297	
New-born haemoglobin (g/dL)		Statistically significant: MD: -4.45 95%CI [-5.33;-3.57] (p<0.00001) *In favour of late cord clamping*	1, 15 vs 30 §	
Infant haemoglobin at 24-48 hours (g/dL)		Statistically significant: MD: -1.40 95%CI [-1.75;-1.05] (p<0.00001) *In favour of late cord clamping*	2, 206 vs 220	
Infant haemoglobin at 3-6		Not statistically significant:	4, 326 vs 355	

months (g/dL)		MD: -0.26 95%CI [-0.79;0.26] (p=0.33)		
Low infant haemoglobin at 3-6 months		Not statistically significant: 42/220 vs 44/218 § RR: 0.96, 95%CI [0.67;1.36] (p=0.81) ¥	2, 220 vs 218	
Infant haematocrit (%) (at 24 hours)		Statistically significant: MD: -4.40 95%CI [-5.71;-3.09] (p<0.00001) *In favour of late cord clamping*	1, 90 vs 90 §	
Infant haematocrit (%) (at 3-5 months)		Not statistically significant: MD: -0.40 95%CI [-1.48;0.68] (p=0.47)	1, 78 vs 82 §	
Infant iron deficiency at 3-6 months		Not statistically significant: 38/214 vs 28/211 § RR: 2.73, 95%CI [0.19;40.19] (p=0.46) ¥	2, 214 vs 211	
Birth weight (g)		Statistically significant: MD: -101.18 95%CI [-157.59;-44.76] (p=0.00044) *In favour of late cord clamping*	12, 1483 vs 1656	
Not breastfeeding on discharge		Not statistically significant: 140/792 vs 139/841 § RR: 1.11, 95%CI [0.90;1.36] (p=0.32) ¥	4, 792 vs 841	
Not breastfeeding at 1 month		Not statistically significant: 82/90 vs 148/178 § RR: 1.10, 95%CI [1.00;1.20] (p=0.052)	1, 90 vs 178	
Not breastfeeding at 2 months		Not statistically significant: 0/41 vs 2/43 § RR: 0.21, 95%CI [0.01;4.24] (p=0.31) ¥	1, 41 vs 43	
Not breastfeeding at 3 months		Not statistically significant: 7/69 vs 8/75 § RR: 0.93, 95%CI [0.36;2.42] (p=0.89) ¥	2, 69 vs 75	
Not breastfeeding at 4 months		Not statistically significant: 102/186 vs 128/205 § RR: 0.88, 95%CI [0.74;1.04] (p=0.13) ¥	2, 186 vs 205	
Not breastfeeding at 6 months		Not statistically significant: 152/208 vs 162/222 RR: 0.99, 95%CI [0.89;1.11] (p=0.21)	2, 208 vs 222	
Neurodevelopment at 4 months		Not statistically significant: MD: -1.40 95%CI [-7.31;4.51] (p=0.64)	1, 180 vs 185 §	
Symptoms of infection during first 4 months (fever)		Not statistically significant: 43/176 vs 49/184 § RR: 0.92, 95%CI [0.64;1.31] (p=0.63) ¥	1, 176 vs 184	
Symptoms of infection during first 4 months (diarrhoea)		Not statistically significant: 16/176 vs 15/184 § RR: 1.12, 95%CI [0.57;2.19] (p=0.75) ¥		

Symptoms of infection during first 4 months (loose stools)		Not statistically significant: 34/176 vs 42/184 § RR: 0.85, 95%CI [0.57;1.27] (p=0.42) ¥		
Symptoms of infection during first 4 months (hard stools)		Not statistically significant: 6/176 vs 8/184 § RR: 0.78, 95%CI [0.28;2.21] (p=0.65) ¥		
Symptoms of infection during first 4 months (belly ache)		Not statistically significant: 45/176 vs 40/184 § RR: 1.18, 95%CI [0.81;1.71] (p=0.39) ¥		
Symptoms of infection during first 4 months (vomiting)		Not statistically significant: 25/176 vs 19/184 § RR: 1.38, 95%CI [0.79;2.41] (p=0.26) ¥		
Symptoms of infection during first 4 months (cough)		Not statistically significant: 63/176 vs 70/184 § RR: 0.94, 95%CI [0.72;1.23] (p=0.66) ¥		
Symptoms of infection during first 4 months (breathing difficulties)		Not statistically significant: 13/176 vs 17/184 § RR: 0.80, 95%CI [0.40;1.60] (p=0.53) ¥		
Symptoms of infection during first 4 months (rhinorrhoea/runny nose)		Not statistically significant: 53/176 vs 59/184 § RR: 0.94, 95%CI [0.69;1.28] (p=0.69) ¥		
Symptoms of infection during first 4 months (nasal congestion)		Not statistically significant: 105/176 vs 103/184 § RR: 1.07, 95%CI [0.89;1.27] (p=0.48) ¥		
Symptoms of infection during first 4 months (otitis)		Not statistically significant: 2/176 vs 3/184 § RR: 0.70, 95%CI [0.12;4.12] (p=0.69) ¥		
Symptoms of infection during first 4 months (rash)		Not statistically significant: 25/176 vs 27/184 § RR: 0.97, 95%CI [0.59;1.60] (p=0.90) ¥		
Symptoms of infection during first 4 months (crying)		Not statistically significant: 51/176 vs 39/184 § RR: 1.37, 95%CI [0.95;1.96] (p=0.091) ¥		
Symptoms of infection during first 4 months (tiredness)		Not statistically significant: 28/176 vs 25/184 § RR: 1.17, 95%CI [0.71;1.93] (p=0.53) ¥		
Symptoms of infection during first 4 months (Visit to paediatrician)		Not statistically significant: 35/176 vs 44/184 § RR: 0.83, 95%CI [0.56;1.23] (p=0.36) ¥		
Symptoms of infection during first 4 months (Visit to other doctor)		Not statistically significant: 16/176 vs 14/184 § RR: 1.19, 95%CI [0.60;2.37] (p=0.61) ¥		

Symptoms of infection during first 4 months (antibiotics)		Not statistically significant: 13/176 vs 10/184 § RR: 1.36, 95%CI [0.61;3.02] (p=0.45) ¥		
Symptoms of infection during first 4 months (admitted to hospital)		Not statistically significant: 14/176 vs 10/184 § RR: 1.46, 95%CI [0.67;3.21] (p=0.34) ¥		

Mean ± SD (unless otherwise indicated)
§ Imprecision (low number of events or limited sample size)
¥ Imprecision (large variability of results)

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See systematic review of McDonald 2013
Imprecision	-1	Limited sample size/low number of events and/or large variability in results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Moderate [B]**	

Conclusion	There is limited evidence in favour of late cord clamping (after 60 seconds of the birth of the infant). In making this evidence conclusion, we place a higher value on the statistically significant outcomes than on the non-statistically significant outcomes. It was shown that delayed cord clamping resulted in a statistically significant increased new-born haemoglobin, infant haemoglobin at 24-48 hours, infant haematocrit and birth weight, compared to early cord clamping (McDonald 2013). A statistically significant difference for 45 other health-related maternal/neonatal outcomes (see table 'synthesis of findings' for details), using early cord clamping compared to late cord clamping, could not be demonstrated (McDonald 2013). Evidence is of moderate quality and results of these studies are imprecise due to the limited sample size/low number of events and/or large variability of results.
Reference(s)	**Systematic reviews** McDonald SJ, Middleton P, Dowswell T, Morris PS. *Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes*. Cochrane Database Syst Rev. 2013, 7:CD004074. **Guideline** NICE guideline. National Collaborating Centre for Women's and Children's Health (UK) 2014. Intrapartum Care: Care of Healthy Women and Their Babies During Childbirth.

Pregnancy and delivery – Antiseptics (First Aid)

Question (PICO)	In new-born babies (P), is the use of antiseptics for cord care (I) effective compared to no application of antiseptics for cord care (C) to direct health-related maternal/neonatal outcomes (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh Anti-Infective Agents, Local] OR "anti-infective":ti,ab,kw OR "anti infective":ti,ab,kw OR "antiinfective":ti,ab,kw OR antiseptic*:ti,ab,kw 2. [mh umbilical Cord] OR 'umbilical cord':ti,ab,kw OR 'umbilical cords':ti,ab,kw 3. 1-2 AND

	Filter: 2004-2015 **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Anti-Infective Agents, Local"[Mesh] OR "anti-infective"[TIAB] OR "anti infective"[TIAB] OR "antiinfective"[TIAB] OR antiseptic*[TIAB] 2. "umbilical Cord"[Mesh] OR "umbilical cord"[TIAB] OR "umbilical cords"[TIAB] 3. 1-3 AND Filter: 2004-2015 **Embase** (via Embase.com interface) using the following search strategy: 1. 'disinfectant agent'/exp OR 'anti-infective':ab,ti OR 'anti infective':ab,ti OR 'antiinfective':ab,ti OR antiseptic*:ab,ti 2. 'umbilical cord'/exp OR 'umbilical cord':ab,ti OR 'umbilical cords':ab,ti 3. 1-3 AND Filter: 2004-2015 Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	13 July 2015
In/Exclusion criteria	**Population:** Include: Live new-borns born to mothers with or without risk factors for the development of infection (for example, chorioamnionitis, preterm rupture of membranes, urinary tract infection), home as place of delivery Exclude: hospital as place of delivery **Intervention:** Include: Antiseptic use (solution or powder) for cord cleansing or total body cleansing. Exclude: a combination of antiseptics and antibiotics. **Comparison:** Include: no antiseptic or placebo/dry cord care. **Outcome:** Include: Direct health-related outcomes (i.e. all-cause mortality, confirmed or suspected sepsis, omphalitis, etc.). Exclude: Indirect health-related outcomes (e.g. bacterial colonization) **Study design:** Include: a systematic review was included if the search strategy and selection criteria are clearly described and if at least MEDLINE and one other relevant database was searched. If no systematic review was published within the last 5 years, individual experimental and/or observational studies were included. Exclude: case series**,** animal studies, *ex vivo* or *in vitro* studies. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline)

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Imdad, 2013, USA	Cochrane systematic review	34 randomized controlled trials involving 69.338 babies	Intervention: antiseptics Control: no antiseptic or placebo/dry cord care	
Sinha, 2015, India	Cochrane systematic review	12 randomized controlled trials (7 hospital-based, 5 community-based)	Intervention: antiseptics (cord or total body) Control: no antiseptic or placebo/dry cord care	
Zupan, 2004	Cochrane systematic review	21 randomized controlled trials (8959 participants)	Intervention: topical cord care Control: no topical care	
Arifeen, 2012, Bangladesh	Experimental: cluster-randomized trial	29760 neonates whose parents were enrolled in the study	Intervention: 4.0% chlorhexidine single application Control: dry care	Cited in systematic review Imdad 2013 and systematic

				review Sinha 2015
Bain, 1994, United Kingdom	Experimental: cluster-randomized trial	102 inborn, premature babies > 1000 g.	Intervention: alcohol wipe (Steret) Control: nothing	Cited in systematic review Zupan 2004
Janssen, 2003, Canada	Experimental: cluster-randomized trial	766 inborn healthy infants	Intervention: triple dye - 2 applications then alcohol thrice daily Control: dry cord care	Cited in systematic review Zupan 2004
Mullany, 2006, Nepal	Experimental: cluster-randomized trial	15113 neonates with first visit within first 10 days of life	Intervention: 4.0% chlorhexidine Control: dry care	Cited in systematic review Imdad 2013 and systematic review Sinha 2015
Pezzati, 2002, Italy	Experimental: cluster-randomized trial	1470 inborn healthy term infants	Intervention 1: salicylic sugar powder Intervention 2: green clay powder Intervention 3: katoxin Intervention 4: 1% basic fuschine Intervention 5: triple dye Intervention 6: 70% alcohol Control: Natural drying	Cited in systematic review Zupan 2004
Soofi, 2012, Pakistan	Experimental: cluster-randomized trial	9741 neonates whose parents were enrolled in the study	Intervention: Chlorhexidine Control: dry care	Cited in systematic review Imdad 2013 and systematic review Sinha 2015

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
All-cause mortality	Cord cleansing with antiseptics vs dry cord care/placebo	Statistically significant: RR: 0.77, 95%CI [0.63; 0.94] (p=0.010) £ *In favour of antiseptics*	3, 16561 vs 17489	Imdad, 2013/Sinha 2015 (Arifeen, 2012, Mullany 2006, Soofi 2012)
Omphalitis (redness extending to skin)		Statistically significant: RR: 0.73, 95%CI [0.64; 0.83] (p<0.00001) £ *In favour of antiseptics*		
Omphalitis (redness with pus or severe redness)		Statistically significant: RR: 0.69, 95%CI [0.60; 0.79] (p<0.00001) £ *In favour of antiseptics*		
Omphalitis (severe redness with pus)		Statistically significant: RR: 0.44, 95%CI [0.28; 0.69] (p=0.00034) £ *In favour of antiseptics*		

Omphalitis	Cord cleansing with alcohol vs dry cord care/placebo	Not statistically significant: 4/202 vs 7/205 § RR: 0.63, 95%CI [0.19; 2.06] (p=0.44) ¥	2, 202 vs 205	Zupan 2004 (Bain 1994, Pezzati 2002)
	Cord cleansing with triple dye vs dry cord care/placebo	Not statistically significant: 2/482 vs 3/486 § RR: 0.68, 95%CI [0.13; 3.49] (p=0.65) ¥	2, 482 vs 486	Zupan 2004 (Janssen 2003, Pezzati 2002)
	Cord cleansing with salicylic sugar powder vs dry cord care/placebo	Not statistically significant: 0/167 vs 2/177 § RR: 0.21, 95%CI [0.01; 4.38] (p=0.32) ¥	1, 167 vs 177	Zupan 2004 (Pezzati 2002)
	Cord cleansing with green clay powder vs dry cord care/placebo	Not statistically significant: 1/184 vs 2/177 § RR: 0.48, 95%CI [0.04; 5.26] (p=0.55) ¥	1, 184 vs 177	Zupan 2004 (Pezzati 2002)
	Cord cleansing with katoxin powder vs dry cord care/placebo	Not statistically significant: 1/208 vs 2/177 § RR: 0.43, 95%CI [0.04; 4.65] (p=0.48) ¥	1, 208 vs 177	Zupan 2004 (Pezzati 2002)
	Cord cleansing with Fuschine vs dry cord care/placebo	Not statistically significant: 1/187 vs 2/177 § RR: 0.47, 95%CI [0.04; 5.17] (p=0.54) ¥	1, 187 vs 177	Zupan 2004 (Pezzati 2002)

Mean ± SD (unless otherwise indicated)
£ No raw data available (generic inverse variance)
¥ Imprecision (large variability of results)
§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Arifeen, 2012	No	Yes	No	No	No
Bain, 1994	Unclear	Unclear	No	No	No
Janssen, 2003	Unclear	Unclear	No	No	No
Mullany, 2006	Unclear	No	No	No	No
Pezzati, 2002	Unclear	Unclear	No	No	No
Soofi, 2012	No	Yes	No	No	Yes, desired sample size was not achieved

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Low number of events and large variability in results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Moderate [B]**	

Conclusion	There is limited evidence in favour of cord cleansing with antiseptics. In making this evidence conclusion, we place a higher value on the statistically significant primary outcomes, which are found by studies with enough power (i.e. higher quality) compared to the studies with non-significant outcomes which have insufficient power (i.e. less quality) It was shown that cord cleansing with antiseptics resulted in a statistically significant decreased all-cause mortality and omphalitis, compared to dry cord care/placebo (Arifeen, 2012, Mullany 2006, Soofi 2012). These studies can be considered as high quality. However, in 1 other study a statistically significant difference in omphalitis, using antiseptics compared to dry cord care/placebo, could not be demonstrated (Pezzati 2002). This study is of moderate quality and results (of the Zupan systematic review) cannot be considered precise due to the low number of events and the large variability of results.
Reference(s)	**Articles** Arifeen SE, Mullany LC, Shah R, Mannan I, Rahman, SM, Talukdar MR, et al. *The effect of cord cleansing with chlorhexidine on neonatal mortality in rural Bangladesh: a community-based cluster-randomized trial*. Lancet 2012, 379(9820):1022–1028. Bain J. *Umbilical cord care in pre-term babies*. Nursing Standard 1994, 8(15):32–36. Janssen PA, Selwood BL, Dobson SR, Peacock D, Thiessen PN. *To dye or not to dye: a randomized clinical trial of a triple dye/alcohol regime versus dry cord care*. Pediatrics 2003, 111(1):15–20. Mullany LC, Darmstadt GL, Khatry SK, LeClerq SC, Katz J, Tielsch JM. I*mpact of umbilical cord cleansing with 4.0% chlorhexidine on time to cord separation among newborns in southern Nepal: a cluster-randomized, community-based trial*. Pediatrics 2006, 118(5):1864–1871. Pezzati M, Biagioli EC, Martelli E, Gambi B, Biagotti R, Rubaltelli FF. *Umbilical cord care: the effect of eight different cord-care regimens on cord separation time and other outcomes*. Biology of the Neonate 2002, 81:38–44. Soofi S, Cousens S, Imdad A, Bhutto N, Ali N, Bhutta ZA. *Topical application of chlorhexidine to neonatal umbilical cords for prevention of omphalitis and neonatal mortality in a rural district of Pakistan: a community-based, clusterrandomized trial*. Lancet 2012, 379:1029–1036. **Systematic reviews** Imdad A, Bautista RMM, Senen KAA, Uy MEV, Mantaring III JB, Bhutta ZA. *Umbilical cord antiseptics for preventing sepsis and death among newborns*. Cochrane Database Syst Rev. 2013, 5:CD008635. Sinha A, Sazawal S, Pradhan A, Ramji S, Opiyo N. Chlorhexidine skin or cord care for prevention of mortality and infections in neonates. Cochrane Database Syst Rev. 2015, 3:CD007835. Zupan J, Garner P, Omari AAA. *Topical umbilical cord care at birth*. Cochrane Database Syst Rev. 2004,3:CD001057.

Pregnancy and delivery – Clinical symptoms (Risk Factor)

Question (PICO)	In new-born (term) infants (P), can some clinical symptoms (RF) considered as a risk factor for the health status of the new-born infant (O)?
Search Strategy	Databases **MEDLINE** (via PubMed interface) for guidelines and systematic reviews using the following search strategy: 1. "Infant, newborn"[Mesh] OR newborn*[TIAB] OR neonate*[TIAB] 2. "Apgar score"[Mesh] OR "Apgar"[TIAB] OR signs[tiab] OR sign[tiab] OR symptom*[tiab] 3. "sensitivity and specificity"[Mesh] OR "sensitivity"[TIAB] OR "specificity"[TIAB] OR "predictive value of tests"[Mesh] OR "false positive"[TIAB] OR "false

negative"[TIAB] OR "accuracy"[TIAB] OR "predictive value"[TIAB] OR "reference values"[Mesh] OR "reference value"[TIAB] OR "reference standard"[TIAB] OR "roc curve"[Mesh] OR "roc"[TIAB] OR "likelihood ratio"[TIAB]

4. "guideline "[Publication Type] OR "Practice Guidelines as Topic"[Mesh] OR "Practice Guideline "[Publication Type] OR practice guideline*[TIAB])) OR Meta-Analysis as Topic[Mesh] OR meta analy*[TIAB] OR metaanaly*[TIAB] OR Meta-Analysis[Publication Type] OR systematic review*[TIAB] OR systematic overview*[TIAB] OR Review Literature as Topic[Mesh] OR cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB])) OR reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB] OR selection criteria[TIAB] OR data extraction[TIAB]
5. 1-4 AND

Embase (via Embase.com interface) for systematic reviews using the following search strategy:

1. 'Newborn'/exp OR newborn*:ab,ti OR neonate*:ab,ti
2. 'Apgar score'/exp OR 'Apgar':ab,ti OR 'signs':ab,ti OR 'sign':ab,ti OR symptom*:ab,ti
3. 'Diagnostic accuracy'/exp OR 'Sensitivity and specificity'/exp OR 'Sensitivity':ab,ti OR 'Specificity':ab,ti OR ((Pre-test or pretest) near/5 probability):ab,ti OR 'Post-test probability':ab,ti OR 'Posttest probability':ab,ti OR 'Predictive value':ab,ti OR 'Predictive values':ab,ti OR 'Likelihood ratio':ab,ti OR 'Likelihood ratios':ab,ti
4. 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti
5. 1-4 AND

The Cochrane Library (systematic reviews) using the following search strategy:

1. [mh infant, newborn] OR newborn*:ti,ab,kw OR neonate*:ti,ab,kw
2. [mh Apgar score] OR signs:ti,ab,kw OR sign:ti,ab,kw OR symptom*:ti,ab,kw OR "Apgar":ti,ab,kw
3. [mh sensitivity and specificity] OR "Sensitivity":ti,ab,kw OR "Specificity":ti,ab,kw OR "Pre-test probability":ti,ab,kw OR "Pretest probability":ti,ab,kw OR "Post-test probability":ti,ab,kw OR "Posttest probability":ti,ab,kw OR "Predictive value":ti,ab,kw OR "Predictive values":ti,ab,kw OR "Likelihood ratio":ti,ab,kw OR "Likelihood ratios":ti,ab,kw
4. MeSH descriptor: [meta-analysis] explode all trees OR meta analys*:ti,ab,kw OR meta-analys*:ti,ab,kw OR 'cochrane':ti,ab,kw OR 'embase':ti,ab,kw OR 'pubmed':ti,ab,kw OR 'medline':ti,ab,kw OR 'reference list':ti,ab,kw OR 'reference lists':ti,ab,kw OR 'bibliography':ti,ab,kw OR 'bibliographies':ti,ab,kw OR 'hand-search':ti,ab,kw OR 'manual search':ti,ab,kw OR 'selection criteria':ti,ab,kw OR 'relevant journals':ti,ab,kw
5. 1-4 AND

MEDLINE (via PubMed interface) for individual studies using the following search strategy:

1. "Infant, newborn"[Mesh] OR newborn*[TIAB] OR neonate*[TIAB]
2. "Apgar score"[Mesh] OR "Apgar"[TIAB]
3. "sensitivity and specificity"[Mesh] OR "sensitivity"[TIAB] OR "specificity"[TIAB] OR "predictive value of tests"[Mesh] OR "false positive"[TIAB] OR "false negative"[TIAB] OR "accuracy"[TIAB] OR "predictive value"[TIAB] OR "reference values"[Mesh] OR "reference value"[TIAB] OR "reference standard"[TIAB] OR "roc curve"[Mesh] OR "roc"[TIAB] OR "likelihood ratio"[TIAB]
4. 1-3 AND

	Embase (via Embase.com interface) for individual studies using the following search strategy: 1. 'Newborn'/exp OR newborn*:ab,ti OR neonate*:ab,ti 2. 'Apgar score'/exp OR 'Apgar':ab,ti OR 'signs':ab,ti OR 'sign':ab,ti OR symptom*:ab,ti 3. 'Diagnostic accuracy'/exp OR 'Sensitivity and specificity'/exp OR 'Sensitivity':ab,ti OR 'Specificity':ab,ti OR ((Pre-test or pretest) near/5 probability):ab,ti OR 'Post-test probability':ab,ti OR 'Posttest probability':ab,ti OR 'Predictive value':ab,ti OR 'Predictive values':ab,ti OR 'Likelihood ratio':ab,ti OR 'Likelihood ratios':ab,ti 4. 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti 5. 1-4 AND **The Cochrane Library** (controlled trials) using the following search strategy: 1. [mh infant, newborn] OR newborn*:ti,ab,kw OR neonate*:ti,ab,kw 2. [mh Apgar score] OR signs:ti,ab,kw OR sign:ti,ab,kw OR symptom*:ti,ab,kw OR "Apgar":ti,ab,kw 3. [mh sensitivity and specificity] OR "Sensitivity":ti,ab,kw OR "Specificity":ti,ab,kw OR "Pre-test probability":ti,ab,kw OR "Pretest probability":ti,ab,kw OR "Post-test probability":ti,ab,kw OR "Posttest probability":ti,ab,kw OR "Predictive value":ti,ab,kw OR "Predictive values":ti,ab,kw OR "Likelihood ratio":ti,ab,kw OR "Likelihood ratios":ti,ab,kw 4. MeSH descriptor: [meta-analysis] explode all trees OR meta analys*:ti,ab,kw OR meta-analys*:ti,ab,kw OR 'cochrane':ti,ab,kw OR 'embase':ti,ab,kw OR 'pubmed':ti,ab,kw OR 'medline':ti,ab,kw OR 'reference list':ti,ab,kw OR 'reference lists':ti,ab,kw OR 'bibliography':ti,ab,kw OR 'bibliographies':ti,ab,kw OR 'hand-search':ti,ab,kw OR 'manual search':ti,ab,kw OR 'selection criteria':ti,ab,kw OR 'relevant journals':ti,ab,kw 5. 1-4 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	15 July 2015
In/Exclusion criteria	**Population:** Include: Full term or late preterm new-born infants (34 to less than 37 completed weeks' gestation), Exclude: Preterm new-born infants (<34 completed weeks' gestation). **Intervention:** Include: Presence of clinical symptoms (such as symptoms related to APGAR-score (Appearance, Pulse, Grimace, Activity, Respiration) **Comparison:** Include: No/less presence of clinical symptoms **Outcome:** Include: direct health-related outcomes (e.g. neonatal mortality) **Study design:** Include: a systematic review was included if the search strategy and selection criteria are clearly described and if at least MEDLINE and one other relevant database was searched. If no systematic review was published within the last 5 years, individual experimental and/or observational studies were included. Exclude: case series**,** animal studies, *ex vivo* or *in vitro* studies. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline)

Characteristics of included studies

Author, year, Country	Study design	Population	Risk factor	Remarks
De Oliveira, 2012, Brazil	Observational: cohort study	7094 new-borns (term infants)	Risk factor: 1-minute APGAR score ≤3 (versus >3), 5-minute APGAR ≤6 (versus >6)	
Moster, 2001, Norway	Observational: cohort study	235.165 children with a birth weight of at least 2500 g	Risk factor: 1-minute APGAR score ≤3 (versus 5-minute APGAR 4-6/7-10), 5-minute APGAR ≤6 (versus >6)	
Verstraete, 2015, Belgium	Systematic review	9 articles with 12 prediction models (observational studies) representing 1295 suspected and 434 laboratory-confirmed sepsis episodes in neonates hospitalized for ≥48 hours.	Risk factor: presence of clinical symptoms (pallor/mottling)	
Weirich, 2005, Brazil	Observational: cohort study	875 new-borns	Risk factor: 5-minute APGAR ≤3 (versus 5-minute APGAR 7-10), 5-minute APGAR 4-6 (versus 5-minute APGAR 7-10)	

Synthesis of findings

Outcome	Risk factor	Effect Size	#studies, # participants	Reference
Neonatal health-care associated sepsis	Pallor/mottling vs no pallor/mottling	Statistically significant: RR: 2.55, 95%CI [1.255;5.183] (p=0.010) £ *In favour of no pallor/mottling*	3, 2554	Verstraete, 2015
Neonatal death	1-minute APGAR score ≤3 vs 1-minute APGAR score >3	Statistically significant: 80/7094 vs 56/7094 § RR: 1.43, 95%CI [1.02;2.02] (p=0.04) * *In favour of 1-minute APGAR score >3*	1, 7094	De Oliveira, 2012
	1-minute APGAR score ≤3 vs 5-minute APGAR score 4-6	Statistically significant: RR: 642, 95%CI [442;934] (p<0.05) £ *In favour of 5-minute APGAR score 4-6*	1, 629	Moster, 2001
	1-minute APGAR score ≤3 vs 5-minute APGAR score 7-10	Statistically significant: RR: 5.8, 95%CI [1.4;24] (p<0.05) £ *In favour of 5-minute APGAR score 7-10*	1, 742	Moster, 2001
	5-minute APGAR score ≤3 versus 5-minute APGAR score 7-10	Statistically significant: Hazard ratio: 2.25, 95%CI [1.29;5.34] (p<0.05) £ *In favour of 5-minute APGAR score 7-10*	1, 875	Weirich, 2005
	5-minute APGAR score 4-6 versus 5-minute APGAR score 7-10	Statistically significant: Hazard ratio: 1.80, 95%CI [1.00;2.45] (p<0.05) £ *In favour of 5-minute APGAR score 7-10*	1, 875	Weirich, 2005
Cerebral palsy	1-minute APGAR score ≤3 vs 5-minute APGAR score 4-6	Statistically significant: No absolute numbers available RR: 57, 95%CI [38;86] (p<0.05) *In favour of 5-minute APGAR score 4-6*	1, 608	Moster, 2001

	1-minute APGAR score ≤3 vs 5-minute APGAR score 7-10	Statistically significant: No absolute numbers available RR: 17, 95%CI [9;32] (p<0.05) *In favour of 5-minute APGAR score 7-10*	1, 733	

£ No absolute numbers available
§ Imprecision (limited sample size)
¥ Imprecision (large variability of results)

Quality of evidence

Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations
De Oliveira, 2012	No	No	Yes	No	No
Moster, 2001	No	No	Yes	No	No
Weirich, 2005	No	No	No	Yes	No

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	0	See systematic review Verstraete 2015 and table 'Quality of evidence'
Imprecision	0	
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	It was shown that pallor/mottling and/or an APGAR-score ≤3 resulted in a statistically significant increased risk of neonatal sepsis (Verstraete, 2005), an increased risk of cerebral palsy (Moster 2001) and an increased risk of neonatal mortality (De Oliveira 2012, Moster 2001, Weirich 2005), compared to no symptoms or to a lesser extent (APGAR scores >4). Evidence is of low quality.
Reference(s)	**Articles** de Oliveira TG, Freire PV, Moreira FT, de Moraes Jda S, Arrelaro RC, Ricardi SR, Juliano Y, Novo NF, Bertagnon JR. *Apgar score and neonatal mortality in a hospital located in the southern area of São Paulo City, Brazil*. Einstein (Sao Paulo). 2012, 10(1):22-28. Moster D, Lie RT, Irgens LM, Bjerkedal T, Markestad T. *The association of Apgar score with subsequent death and cerebral palsy: A population-based study in term infants.* J Pediatr. 2001, 138(6):798-803. Weirich CF, Andrade AL, Turchi MD, Silva SA, Morais-Neto OL, Minamisava R, Marques SM. *Neonatal mortality in intensive care units of Central Brazil.* Rev Saude Publica. 2005, 39(5):775-781. **Systematic reviews** Verstraete EH, Blot K, Mahieu L, Vogelaers D, Blot S. *Prediction models for neonatal health care-associated sepsis: a meta-analysis*. Pediatrics. 2015, 135(4):e1002-1014.

Pregnancy and delivery – Breast feeding (First Aid)

Question (PICO)	In women who have given birth to a (pre-)term infant (P), is early breast feeding (I) effective to improve the birth of the placenta and to decrease the risk of post-partum haemorrhage (O)?
Search Strategy	Databases **The Cochrane Library** using the following search strategy: 1. [mh "breast feeding"] OR "breastfeeding":ti,ab,kw OR "breast feeding":ti,ab,kw OR "nipple stimulation":ti,ab,kw 2. [mh "placenta"] OR [mh "postpartum haemorrhage"] OR "placenta":ti,ab,kw OR "postpartum haemorrhaege":ti,ab,kw OR "post-partum haemorrhage":ti,ab,kw OR "postpartum hemorrhage":ti,ab,kw OR "post-partum hemorrhage":ti,ab,kw OR "postpartum haematoma":ti,ab,kw OR "post-partum haematoma":ti,ab,kw OR "postpartum hematoma":ti,ab,kw OR "post-partum hematoma":ti,ab,kw 3. [mh "infant, newborn"] OR newborn*:ti,ab,kw OR neonate*:ti,ab,kw OR [mh "pregnancy"] OR "pregnancy":ti,ab,kw 4. 1-3 AND **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Breast feeding"[Mesh] OR "breastfeeding"[TIAB] OR "breast feeding"[TIAB] OR "nipple stimulation"[TIAB] 2. "placenta"[Mesh] OR "postpartum haemorrhage"[Mesh] OR "placenta"[TIAB] OR "postpartum haemorrhaege"[TIAB] OR "post-partum haemorrhage"[TIAB] OR "postpartum hemorrhage"[TIAB] OR "post-partum hemorrhage"[TIAB] OR "postpartum haematoma"[TIAB] OR "post-partum haematoma"[TIAB] OR "postpartum hematoma"[TIAB] OR "post-partum hematoma"[TIAB] 3. "Infant, newborn"[Mesh] OR newborn*[TIAB] OR neonate*[TIAB] OR "Pregnancy"[Mesh] OR pregnancy[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'Breast feeding'/exp OR 'breastfeeding':ab,ti OR 'breast feeding':ab,ti OR 'nipple stimulation':ab,ti 2. 'placenta'/exp OR 'postpartum haemorrhage'/exp OR 'placenta':ab,ti OR 'postpartum haemorrhaege':ab,ti OR 'post-partum haemorrhage':ab,ti OR 'postpartum hemorrhage':ab,ti OR 'post-partum hemorrhage':ab,ti OR 'postpartum haematoma':ab,ti OR 'post-partum haematoma':ab,ti OR 'postpartum hematoma':ab,ti OR 'post-partum hematoma':ab,ti 3. 'Newborn'/exp OR newborn*:ab,ti OR neonate*:ab,ti OR pregnancy:ab,ti OR 'pregnancy'/exp 4. 1-3 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	14 July 2015
In/Exclusion criteria	**Population:** Included: women who have given birth to a (pre-)term infant **Intervention:** Include: early breast feeding **Comparison:** Include: bottle feeding or late/delayed breast feeding **Outcome:** Include: direct health-related outcomes related to the mother (maternal outcomes), i.e. birth of placenta and postpartum haemorrhage. **Study design:** Include: a systematic review was included if the search strategy and selection criteria are clearly described and if at least MEDLINE and one other relevant database was searched. If no systematic review was published within the last 5 years, individual experimental and/or observational studies were included. Exclude: case series**,** animal studies, *ex vivo* or *in vitro* studies.

	Language: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: All years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Bullough, 1989, United Kingdom	Experimental: randomized controlled trial	4271 deliveries who were attended by traditional birth attendants (who have received a 4-week training, which includes instruction in carrying out normal deliveries and the recognition of risk factors during antenatal care and in labour.). Randomisation of the traditional birth attendants took place (rather than the mothers).	Intervention: suckling group: breastfeeding immediately after birth Control: usual care (delayed breastfeeding, i.e. after some hours)	Malawian women do not breast-feed their babies immediately after birth. It is commonly believed that the mother is tired after delivery and requires rest, and that the baby does not need an immediate feed. After being dried and wrapped, the baby is initially cared for by a relative. The mother rests, is given a wash or helped to shower, and then after some hours will first breastfeed. The third stage of labour is defined as the delivery of the placenta within 5 to 15 minutes after the baby arrives.
Irons, 1994, UK	Experimental: randomized controlled trial	14 women for whom a spontaneous vaginal delivery was anticipated The following groups were excluded from the study: postpartum haemorrhage or retained placenta in a previous pregnancy; antepartum haemorrhage; multiple pregnancy; prolonged labour (over 16 h); anaemia (Hb < 10 g/dl); oxytocin infusion or operative delivery in the current pregnancy.	1. routine syntometrine injection 2. bilateral nipple stimulation, immediately after delivery 3. no treatment [only data about nipple stimulation were extracted] Instructions were that nipple stimulation should begin immediately after delivery and be bilateral. The mothers were instructed to compress the nipple between two fingers intermittently, mimicking the action and frequency of	Nipple stimulation is seen as an indirect intervention to mimic breastfeeding

			suckling. They were asked to continue nipple stimulation for 15 min.	
Sobhy, 2004, USA	Experimental: non-randomized controlled trial	one hundred primiparae (20-35 years) Mothers having normal delivery. normal breast with protruded nipple, having no complicated third stage of labour, and giving birth to full term new-born with no congenital anomalies interfering with, breast-feeding were included in the study.	1. early breastfeeding (immediately after placental delivery, n= 50) Each new-born was put on the breast for at least 15 minutes for 2-4 times throughout the first 2 postpartum hours. 2. late breastfeeding (after the first two hours postnatally, n=50)	A specially designed interview questionnaire was used during early first stage of labour to collect data about general characteristics of the study subjects. An observational checklist was used during the fourth stage of labour to collect data about uterine characteristics, number of feeds and the amount of blood loss. The fourth stage of labour is defined as the hour or two after delivery when the tone of the uterus is re-established as the uterus contracts again, expelling any remaining contents.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Postpartum haemorrhage (>500 ml blood loss during the third stage of labour or within the first 24 h after delivery)	Early versus late breastfeeding	Not statistically significant: 167/2114 vs 178/2119 RR: 0.94, 95%CI [0.77;1.15] (p=0.55) *	1, 2114 vs 2119	Bullough, 1989
Retained placenta		Not statistically significant: 2/2114 vs 2/2119 § RR: 1.00, 95%CI [0.14;7.11] (p=1.00) * ¥		
Fundal level below umbilicus		Statistically significant: 34/50 vs 18/50 § RR: 1.89, 95%CI [1.25;2.86] (p=0.0005) * *In favour of early breastfeeding*	1, 50 vs 50	Sobhy, 2004
Uterine consistency firm		Statistically significant: 41/50 vs 27/50 §		

		RR: 1.52, 95%CI [1.14;2.02] (p=0.004) * *In favour of early breastfeeding*		
Vaginal blood loss > 250 ml		Statistically significant: 17/50 vs 37/50 § RR: 0.46, 95%CI [0.30;0.70] (p=0.0003) * *In favour of early breastfeeding*		
Frequency of contractions	Immediate nipple stimulation vs no nipple stimulation	Not statistically significant: 202 vs 179 £ †	1, 6 vs 5 §	Irons, 1994
Peak placental venous pressure during contractions (mmHg)		Statistically significant: 103.0 vs 70.8 £ † (p=0.04) *In favour of immediate nipple stimulation*		
Blood loss (ml)		Not statistically significant: 166 vs 257 £ †		

£ No SD's available, effect size and CI cannot be calculated
§ Imprecision (low number of events or limited sample size)
¥ Imprecision (large variability of results)
† Imprecision (lack of data)
* Calculations done by the reviewer(s) using Review Manager software

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Bullough, 1989	Yes	No	No	Yes	No
Irons, 1994	No	Unclear	No	No	No
Sobhy, 2004	Yes	Unclear	No	No	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	(except for outcome postpartum haemorrhage in Bullough, 1989)
Inconsistency	0	
Indirectness	-1	Nipple stimulation is an intervention to mimic breastfeeding
Publication bias	0	
QUALITY (GRADE)	**Final grading Low[C] to very low [D]**	

Conclusion	There is limited evidence in favour of early breast feeding (i.e. immediately after birth). In making this evidence conclusion, we place a higher value on the statistically significant outcomes over the non-statistically significant outcomes. It was shown that early breast feeding resulted in a statistically significant increase of the fundal level being below the umbilicus and the uterine consistency being firm, and a statistically significant decrease of the vaginal blood loss > 250 ml, compared to delayed breast feeding (Sobhy 2004). In another study it was shown that nipple stimulation immediately after delivery, an intervention to mimic early breast feeding, resulted in a statistically significant decrease of peak placental venous pressure during contractions (which will result in a reduction in the incidence of postpartum haemorrhage), compared to no nipple stimulation (Irons 1994). A statistically significant decrease of the frequency of contractions and amount of blood loss could not be demonstrated (Irons 1994).

	In a third study it was shown that early breast feeding did not result in a statistically significant decrease of postpartum haemorrhage (blood loss > 500 ml) compared to late breast feeding (Bullough 1989). A statistically significant difference in the frequency of a retained placenta, in case of early breast feeding compared to late early breast feeding, could not be demonstrated (Bullough 1989). Evidence is of low (early breast feeding) to very low (nipple stimulation) quality and results of these studies are imprecise due to limited sample size, low number of events or large variability of results.
Reference(s)	**Articles** Bullough CH, Msuku RS, Karonde L. *Early suckling and postpartum haemorrhage: controlled trial in deliveries by traditional birth attendants*. Lancet 1989, 2(8662):522-525 Irons DW, Sriskandabalan P, Bullough CH. *A simple alternative to parenteral oxytocics for the third stage of labor*. Int J Gynaecol Obstet 1994, 46(1):15-8 Sobhy SI, Mohame NA. *The effect of early initiation of breast feeding on the amount of vaginal blood loss during the fourth stage of labor*. J Egypt Public Health Assoc. 2004, 79(1-2):1-12

Pregnancy and delivery – Massage (First Aid)

Question (PICO)	In women (P), is massage (I) compared to usual care (C) effective for pain or other health-related outcomes during labour (C)?
Search Strategy	The starting point for this PICO was the NICE guideline 2014 entitled 'Intrapartum care: care of healthy women and their babies during childbirth'. This guideline includes a Cochrane systematic review of 2012 which addressed this PICO question and was used as source of individual studies. Therefore, the search strategies below aimed to find additional experimental studies (i.e. randomized controlled trials) from 2012 until 7/07/2015. Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh Labor, Obstetric/adverse effects] OR [mh Labor, Obstetric/mortality] OR [mh Labor, Obstetric/physiology] OR [mh Labor, Obstetric/physiopathology] OR [mh Labor, Obstetric/prevention and control] OR [mh Labor, Obstetric/therapeutic use] OR [mh Labor, Obstetric/therapy] OR labor:ti,ab,kw OR [mh Parturition/adverse effects] OR [mh Parturition/injuries] OR [mh Parturition/mortality] OR [mh Parturition/physiology] OR [mh Parturition/psychology] OR [mh Parturition/rehabilitation] OR [mh Parturition/therapeutic use] OR [mh Parturition/therapy] OR parturition:ti,ab,kw 2. [mh massage] OR massage:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Labor, Obstetric/adverse effects"[Mesh] OR "Labor, Obstetric/mortality"[Mesh] OR "Labor, Obstetric/physiology"[Mesh] OR "Labor, Obstetric/physiopathology"[Mesh] OR "Labor, Obstetric/prevention and control"[Mesh] OR "Labor, Obstetric/therapeutic use"[Mesh] OR "Labor, Obstetric/therapy"[Mesh] OR "labor"[TIAB]) OR "Parturition/adverse effects"[Mesh] OR "Parturition/injuries"[Mesh] OR "Parturition/mortality"[Mesh] OR "Parturition/physiology"[Mesh] OR "Parturition/psychology"[Mesh] OR "Parturition/rehabilitation"[Mesh] OR "Parturition/therapeutic use"[Mesh] OR "Parturition/therapy"[Mesh] OR parturition[TIAB] 2. "Massage"[Mesh] OR "massage"[TIAB] 3. 1-2 AND

	Embase (via Embase.com interface) using the following search strategy: 1. 'labor'/exp OR 'birth'/exp OR 'labor':ab,ti OR 'birth':ab,ti 2. 'massage'/exp OR 'massage':ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	07 July 2015
In/Exclusion criteria	**Population:** Include: women in labour. **Intervention:** Include: Massage of superficial soft tissue (skin, muscles). Exclude: massage techniques which cannot be performed by laypeople (e.g. perineal massage) **Comparison:** Include: placebo, no treatment, usual care Exclude: other methods of pain management (hypnosis, biofeedback, intracutaneous or subcutaneous water injection, immersion in water, aromatherapy, relaxation techniques (yoga, music, audio) or acupuncture or acupressure. **Outcome:** Include: Pain and other direct health-related outcomes **Study design:** Include: a systematic review was included if the search strategy and selection criteria are clearly described and if at least MEDLINE and one other relevant database was searched. If no systematic review was published within the last 5 years, individual experimental and/or observational studies were included. Exclude: case series**,** animal studies, *ex vivo* or *in vitro* studies. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline)

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Hajiamini, 2012, Iran	Experimental: randomized controlled trial	90 pregnant women referred from selected hospitals in Tehran (mean age of 27.82±6.20 years). Subjects were excluded if they had any underlying renal or cardiovascular disease, gestational diabetes, pre eclampsia, mental disorders, visual impairments, or a history of acupressure.	Intervention: Ice massage (after identifying the Hegu point on the hand, ice massage was performed with the researcher placing ice balls (2 cm in diameter) inside a wet thin gauze into the hand and massaging rotationally for 10 min (2 min pressure and 15 min break) Control: Placebo (ice balls were used at the same point but without pressure or massage)	
Mortavazi, 2012, Iran	Experimental: randomized controlled trial	120 primiparous women (mean age of 23) experiencing a normal pregnancy without any complications, term pregnancy at the time of admission	Intervention: Massage: Firm and rhythmic massage for 30 min in three phases: latent phase (3–4 cm cervical dilation), active phase (5–7 cm cervical dilation), and	

		(gestational age between 37 and 42 weeks) and cervical dilatation of no more than 4 cm. Exclusion criteria were needing to caesarean section for any medical reason and also Oxytocin infusion to accelerate or augment labour progression.	deceleration phase (8–10 cm cervical dilation). Massages included shoulder and back massage, abdominal effleurage and sacral pressure. Control: usual care	
Silva Gallo, 2013, Brazil	Experimental: randomized controlled trial	46 women pregnant at ≥37 weeks gestation with a single foetus, with spontaneous onset of labour, 4–5 cm of cervical dilation, intact ovular membranes, and no use of medication after admission to hospital.	Intervention: a 30-min lumbar massage by a physiotherapist during the active phase of labour Control: usual care (30 minutes attention with only answering questions)	
Smith, 2012, Australia	Cochrane systematic review of 6 randomized controlled trials	Women in labour. Four studies recruited primiparous women only, and at term (Abasi 2009; Chang 2002; Karami 2007; Taghinejad 2010). One study recruited women between 35 and 37 weeks' gestation (Kimber 2008), and the characteristics of women in one study (Field 1997) study were not reported.	Intervention: Massage. There was variation in the frequency, duration and technique in how the massage was applied. Control: Standard/usual care	Abasi 2009: Back massage was continuous, firm and steady for 30 minutes during each phase of labour. Massage applied from sacral spine upward to the lumbar spine, then back down to the sacrum. A masseuse applied the intervention. Chang 2002: Received directional, reasonably firm and rhythmic massage for 30minutes and comprising abdominal effleurage, sacral pressure and shoulder and back kneading Field 1997: 20 minutes of head, shoulder/back, hand and foot massage. Karami 2007: The massage

				is administered on sacrum, buttocks, shoulders, waist, foot and hand during different phases of labour <u>Kimber 2008:</u> Birth partner was learnt to perform slow rhythmic long stroke massage movements using the flats of the hands. These strokes were combined with slow rhythmic breathing and performed primarily on the lower back and also the upper and lower limbs. <u>Taghinejad 2010:</u> Massage points were the lower area of the abdomen, shoulders, back and pressed pubic area. All received 30 minutes of massage

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Pain intensity (first stage of labour)	Massage vs usual care	<u>Statistically significant:</u> SMD: -0.82, 95%CI [-1.17;-0.47] (p<0.00001) *In favour of massage*	4, 106 vs 119 §	Smith 2012
Pain intensity (first (active) phase)		<u>Statistically significant:</u> 52±20 vs 72±15 MD: -20, 95%CI [-10;-31] (p=0.0001) *In favour of massage*	1, 23 vs 23 §	Silva Gallo, 2013
Pain intensity (second stage of labour)		Not statistically significant: SMD: -0.98, 95%CI [-2.23;0.26] (p=0.12)	2, 62 vs 62 §	Smith, 2012
Pain intensity (third stage of labour)		Not statistically significant: SMD: -1.03, 95%CI [-2.18;0.11] (p=0.08)	2, 62 vs 60 §	
Pain state (first-second-third stage of labour)		<u>Statistically significant (lower):</u> (p<0.05) £ *In favour of massage*	1, 40 vs 40 §	Mortavazi, 2012
Anxiety level		<u>Statistically significant (lower):</u> (p<0.05) £ *In favour of massage*		
Length of labour		Not statistically significant: SMD: 0.34, 95%CI [-0.07;0.75] (p=0.10) ££†	2, 42 vs 55 §	Smith, 2012

Length of active phase (hours)		Statistically significant: 2.6±0.95 vs 7.5±1.87 MD: -4.90, 95%CI [-5.55;-4.25] (p<0.00001) * *In favour of massage*	1, 40 vs 40 §	Mortavazi, 2012
Anxiety (first stage)		Statistically significant: 37.2±20.3 vs 53.47±22.18 SMD: -16.27, 95%CI [-27.03;-5.51] (p=0.003) *In favour of massage*	1, 30 vs 30 §	Smith 2012
Anxiety (second stage)		Not statistically significant: 64.9±24.07 vs 73.87±22.64 SMD: -8.97, 95%CI [-20.79;2.85] (p=0.14)		
Anxiety (third stage)		Not statistically significant: 80.6±19.11 vs 85.17±18.29 SMD: -4.57, 95%CI [-14.04;4.90] (p=0.34)		
Pain intensity (immediate after delivery)	Ice massage versus placebo	Not statistically significant: 5.73±1.74 vs 6.33±1.72 MD: -0.60, 95%CI [-1.48;0.28] (p=0.18)*	1, 30 vs 30 §	Hajiamini, 2012
Pain intensity (30 minutes after delivery)		Statistically significant: 5.90±1.84 vs 7.10±1.64 MD: -1.20, 95%CI [-2.08;-0.32] (p=0.008)* *In favour of ice massage*		
Pain intensity (60 minutes after delivery)		Not statistically significant: 6.77±1.97 vs 7.60±1.56 MD: -0.83, 95%CI [-1.73;0.07] (p=0.07)*		

Mean ± SD (unless otherwise indicated)
£ No raw data/CI/effect size available
££ No raw data available
§ Imprecision (limited sample size)
† Imprecision (lack of data)
* Calculations done by the reviewer(s) using Review Manager software

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Hajiamini, 2012	unclear	yes	no	no	
Mortavazi, 2012	unclear	yes	no	no	
Silva Gallo, 2013	no	no	no	no	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See 'Quality of evidence' and systematic review of Smith 2012
Imprecision	-1	Limited sample size
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	Pain intensity

	There is limited evidence in favour of massage. It was shown that massage resulted in a statistically significant decreased pain intensity (during first/second/third stage of labour), compared to usual care (Mortavazi 2012, Gallo 2013, Smith 2012). However, 2 studies were not able to demonstrate a statistical significant difference in pain intensity during the second and third stage of labour (2 studies cited in Smith 2012). Evidence is of low quality and results cannot be considered precise due to limited sample size. There is limited evidence neither in favour of ice massage on a pressure point on the hand nor usual care. In making this evidence conclusion, we place a higher value on short (immediately after birth) and longer term (60 minutes after birth) over intermediate term (30 minutes after birth) outcomes. Using ice massage compared to usual care, a statistically significant decreased pain intensity could not be demonstrated (Hajiamini, 2012) immediately after and 60 minutes after birth while pain intensity was statistically significantly lower 30 minutes after birth. Evidence is of low quality and results of this study are imprecise due to limited sample size. **Anxiety** There is limited evidence in favour of massage. It was shown that massage resulted in a statistically significant decrease of anxiety during the first stage of labour, compared to usual care (Smith 2012, Mortavazi 2012). However, a statistical significant difference in anxiety during the second and third stage of labour when performing massage compared to usual care could not be demonstrated (1 study cited in Smith 2012). Evidence is of low quality and results cannot be considered precise due to limited sample size. **Length of labour** There is limited evidence in favour of massage. In making this evidence conclusion, we place a higher value on the length of the active phase of labour (MD: about 5 hours) over the total length of labour (MD: about 30 minutes). It was shown that massage resulted in a statistically significant decreased duration of the active phase of labour, compared to usual care (Mortavazi, 2012). However, a statistical significant difference in the total duration of labour, when performing massage compared to usual care, could not be demonstrated (2 studies cited in Smith 2012). Evidence is of low quality and results cannot be considered precise due to the limited sample size.
Reference(s)	**Articles** Hajiamini Z, Masoud SN, Ebadi A, Mahboubh A, Matin A. *Comparing the effects of ice massage and acupressure on labor pain reduction.* Complementary Therapies in Clinical Practice 2012, 18:169-172. Mortazavi SH, Khaki S, Moradi R, Heidari K, Rahimparvar SFV. *Effects of massage therapy and presence of attendant on pain, anxiety and satisfaction during labor.* Arch Gynecol Obstet 2012, 286:19–23. Gallo RBS, Santana LS, Ferreira CHJ, Marcolin AC, PoliNeto OB, Duarte G, Quintana SM. *Massage reduced severity of pain during labour: a randomised trial.* Journal of Physiotherapy 2013, 59: 109-116. **Systematic review** Smith CA, Levett KM, Collins CT, Jones L. *Massage, reflexology and other manual methods for pain management in labour*. Cochrane Database Syst Rev 2012, 15;2:CD009290. **Guideline**

	NICE guideline. National Collaborating Centre for Women's and Children's Health (UK) 2014. Intrapartum Care: Care of Healthy Women and Their Babies During Childbirth.

Pregnancy and delivery – Restriction of fluids and food (First Aid)

Question (PICO)	In women during the labor of an emergency delivery (P), is the restriction of fluids and food (I) effective compared to free eating and drinking (C) with respect to maternal/fetal health-related outcomes (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh meta-analysis] OR meta analys*:ti,ab,kw OR meta-analys*:ti,ab,kw OR 'cochrane':ti,ab,kw OR 'embase':ti,ab,kw OR 'pubmed':ti,ab,kw OR 'medline':ti,ab,kw OR 'reference list':ti,ab,kw OR 'reference lists':ti,ab,kw OR 'bibliography':ti,ab,kw OR 'bibliographies':ti,ab,kw OR 'hand-search':ti,ab,kw OR 'manual search':ti,ab,kw OR 'selection criteria':ti,ab,kw OR 'relevant journals':ti,ab,kw 2. [mh Labor, Obstetric/adverse effects] OR [mh Labor, Obstetric/mortality] OR [mh Labor, Obstetric/physiology] OR [mh Labor, Obstetric/physiopathology] OR [mh Labor, Obstetric/prevention and control] OR [mh Labor, Obstetric/therapeutic use] OR [mh Labor, Obstetric/therapy] OR labor:ti,ab,kw OR [mh Parturition/adverse effects] OR [mh Parturition/injuries] OR [mh Parturition/mortality] OR [mh Parturition/physiology] OR [mh Parturition/psychology] OR [mh Parturition/rehabilitation] OR [mh Parturition/therapeutic use] OR [mh Parturition/therapy] OR parturition:ti,ab,kw 3. [mh food] OR food:ti,ab,kw OR eat*:ti,ab,kw OR drink*:ti,ab,kw 4. 1-3 AND **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Guideline "[Publication Type] OR "Practice Guidelines as Topic"[Mesh] OR "Practice Guideline "[Publication Type] OR practice guideline*[TIAB] OR Meta-Analysis as Topic[Mesh] OR meta analy*[TIAB] OR metaanaly*[TIAB] OR Meta-Analysis[Publication Type] OR systematic review*[TIAB] OR systematic overview*[TIAB] OR Review Literature as Topic[Mesh] OR cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB] OR reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB] OR selection criteria[TIAB] OR data extraction[TIAB] AND Review[PT] 2. "Labor, Obstetric/adverse effects"[Mesh] OR "Labor, Obstetric/mortality"[Mesh] OR "Labor, Obstetric/physiology"[Mesh] OR "Labor, Obstetric/physiopathology"[Mesh] OR "Labor, Obstetric/prevention and control"[Mesh] OR "Labor, Obstetric/therapeutic use"[Mesh] OR "Labor, Obstetric/therapy"[Mesh] OR "labor"[TIAB]) OR "Parturition/adverse effects"[Mesh] OR "Parturition/injuries"[Mesh] OR "Parturition/mortality"[Mesh] OR "Parturition/physiology"[Mesh] OR "Parturition/psychology"[Mesh] OR "Parturition/rehabilitation"[Mesh] OR "Parturition/therapeutic use"[Mesh] OR "Parturition/therapy"[Mesh] OR parturition[TIAB] 3. Food[Mesh] OR food[TIAB] OR eat*[TIAB] OR drink*[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR

	'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti 2. 'labor'/exp OR 'birth'/exp OR 'labor':ab,ti OR 'birth':ab,ti 3. Food/exp OR food:ab,ti OR eat*:ab,ti OR drink*:ab,ti 4. 1-3 AND Guidelines, systematic reviews, retrieved with the above searches, and used as source for individual studies: Singata, 2013 Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	07 July 2015
In/Exclusion criteria	**Population:** Include: women in labour. **Intervention:** Include: Studies comparing any two or more of the following regimens for inclusion. 1. Complete restriction of oral food and fluids (other than ice chips). 2. Allowing only water. 3. Allowing only oral carbohydrate-based fluids. 4. Allowing particular oral food and fluid regimens. 5. Freedom to take oral food and/or fluids at will. Exclude: intravenous feeding in labour unless being given on a clinical need within a study on oral fluids and food **Outcome:** Include: *Primary outcomes*: Maternal outcomes (caesarean section, operative vaginal birth, maternal satisfaction) and foetal outcomes (Five-minute Apgar score less than seven, hypoglycaemia). *Secondary outcomes*: Maternal outcomes (ketoacidosis, dehydration, hyponatremia, hypoglycaemia, duration of labour, mobility in labour, nausea and vomiting, labour augmentation, narcotic pain relief, poor expulsive efforts, maternal mortality, postpartum haemorrhage, feelings of pain, thirst, hunger, breastfeeding success, personal control. Foetal outcomes: foetal distress, cord blood pH less than 7.2, hyperinsulinisim, hyponatraemia. **Study design:** Include: a systematic review was included if the search strategy and selection criteria are clearly described and if at least MEDLINE and one other relevant database was searched. If no systematic review was published within the last 5 years, individual experimental and/or observational studies were included. Exclude: case series**,** animal studies, *ex vivo* or *in vitro* studies. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication Year:** Include: All years.

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Singata, 2013	Cochrane systematic review	5 randomized controlled trials involving 3130 women in labour	Intervention: restricting fluids and food Control: free to eat and drink	
Kubli, 2002, United Kingdom	Experimental: randomized controlled trial	60 women at low risk of complications in early labour (> 37 weeks; singleton; cephalic; < 5 cm dilatation) Excluded: obstetric or medical complication; increased likelihood OVB or CS; mothers requesting IM meperidine	Intervention: water only, as much as desired. Comparison: isotonic sports drink (dextrose, maltolactose, glucose, 28 kcal/dL), women encouraged to drink 500 mL in 1st hour and further	cited in SR Singata 2013, sample size calculation was not done

			500 mL every 3-4 hours. Small quantities of water were also available if desired	
O'Sullivan, 2009, United Kingdom	Experimental: randomized controlled trial	2443 women in labour at low risk of complications (no known obstetric or medical complication that would increase the likelihood of operative birth; nulliparous; singleton; cephalic; > 36 weeks; no diabetes; but included induction and augmentation); also women were < 6 cm	Intervention: water and ice chips only. Comparison: specific foods and fluids encouraged (women advised to consume low fat, low-residue diet at will during labour). Foods advised were: bread, biscuits, vegetables, fruits, low fat yoghurt, soup, isotonic drinks and fruit juice	cited in SR Singata 2013, sample size calculation was done
Scheepers, 2002, The Netherlands	Experimental: randomized controlled trial	203 nulliparous women in early labour (singleton; cephalic; 2-4 cm dilatation)	Intervention: flavoured water (artificial aroma, aspartame, acesulfame), as much as desired Comparison: carbohydrate drink (per 100 mL: 12.6 g carbohydrates: 9.8% polysach/Na: 50 mg, Osm: 280 mOsm/L), as much as desired	cited in SR Singata 2013, sample size calculation was done
Scrutton, 1999, United Kingdom	Experimental: randomized controlled trial	94 women at low risk of complications in early labour (> 37 weeks; singleton; cephalic; < 5 cm dilatation)	Intervention: water only. Comparison: low residue food (women were allowed to select from a low-residue diet throughout the course of labour)	cited in SR Singata 2013, sample size calculation was done
Tranmer, 2005, Canada	Experimental: randomized controlled trial	330 women at low risk of complications (> 30 weeks; singleton; no recorded maternal or foetal complication)	Intervention: ice chips and sips water Comparison: unrestricted access to their choice of food and fluids during labour	cited in SR Singata 2013, sample size calculation was done

Synthesis of findings

Outcome	Comparison/Risk factor	Effect Size	#studies, # participants	Reference
Maternal outcomes				
Caesarean section	Any restriction of oral fluid and food versus some fluid and food	Not statistically significant: 422/1544 vs 439/1559 RR: 0.89, 95%CI [0.63; 1.25] (p=0.49) ¥	5, 1544 vs 1559	Singata, 2013
	Complete restriction of oral fluid and food versus freedom to eat and drink	Not statistically significant: 32/165 vs 41/163 § RR: 0.77, 95%CI [0.51; 1.16] (p=0.21) ¥	1, 165 vs 163	

Operative vaginal birth	Any restriction of oral fluid and food versus some fluid and food	Not statistically significant: 416/1544 vs 428/1559 RR: 0.98, 95%CI [0.88; 1.10] (p=0.77)	5, 1544 vs 1559	
	Complete restriction of oral fluid and food versus freedom to eat and drink	Not statistically significant: 53/165 vs 53/163 § RR: 0.99, 95%CI [0.72; 1.35] (p=0.94) ¥	1, 165 vs 163	
Maternal ketoacidosis	Any restriction of oral fluid and food versus some fluid and food	Not statistically significant: 36/165 vs 36/163 § RR: 0.99, 95%CI [0.66; 1.49] (p=0.95) ¥	1, 165 vs 163	
	Complete restriction of oral fluid and food versus freedom to eat and drink	Not statistically significant: 36/165 vs 36/163 § RR: 0.99, 95%CI [0.66; 1.49] (p=0.95) ¥		
Duration of labour (hours)	Any restriction of oral fluid and food versus some fluid and food	Not statistically significant: MD: -0.29, 95%CI [-1.55; 0.97] (p=0.65)	3, 238 vs 238	
	Complete restriction of oral fluid and food versus freedom to eat and drink	Not statistically significant: MD: -0.80, 95%CI [-2.13; 0.53] (p=0.24)	1, 165 vs 163	
Maternal nausea	Any restriction of oral fluid and food versus some fluid and food	Not statistically significant: 34/133 vs 39/122 § RR: 0.80, 95%CI [0.54; 1.18] (p=0.26) ¥	1, 133 vs 122	
	Complete restriction of oral fluid and food versus freedom to eat and drink	Not statistically significant: 34/133 vs 39/122 § RR: 0.80, 95%CI [0.54; 1.18] (p=0.26) ¥		
Maternal vomiting	Any restriction of oral fluid and food versus some fluid and food	Not statistically significant: 428/1280 vs 402/1294 RR: 0.90, 95%CI [0.62; 1.31] (p=0.60) ¥	3, 1280 vs 1294	
Augmentation of labour		Not statistically significant: 837/1544 vs 817/1559 RR: 1.02, 95%CI [0.95; 1.09] (p=0.58)	5, 1544 vs 1559	
Augmentation of labour	Complete restriction of oral fluid and food versus freedom to eat and drink	Not statistically significant: 91/165 vs 92/163 § RR: 0.98, 95%CI [0.81; 1.18] (p=0.81)	1, 165 vs 163	
Narcotic pain relief		Not statistically significant: 100/172 vs 115/177 § RR: 0.94, 95%CI [0.74; 1.21] (p=0.65)	3, 172 vs 177	
Foetal outcomes				
Apgar <7 at 5 min	Any restriction of oral fluid and food versus some fluid and food	Not statistically significant: 23/1445 vs 16/1457 § RR: 1.43, 95%CI [0.77; 2.68] (p=0.26) ¥	4, 1445 vs 1457	Singata, 2013

¥ Imprecision (large variability of results)

§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Kubli, 2002	Unclear	Yes	No	No	
O'Sullivan, 2009	No	Yes	No	No	
Scheepers, 2002	No	No	No	No	
Scrutton, 1999	Unclear	Yes	No	No	
Tranmer, 2005	No	Yes	No	No	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Low number of events
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Moderate [B]**	

Conclusion	There is limited evidence neither in favour of any/complete restriction of oral fluid and food nor some fluid and food/freedom to eat and drink. A statistically significant improvement in health-related maternal/fetal outcomes, using any/complete restriction of oral fluid and food compared to some fluid and food/freedom to eat and drink, could not be demonstrated (Singata 2013). Evidence is of moderate quality and results of this systematic review are imprecise due to the low number of events.
Reference(s)	**Articles** Kubli M, Scrutton MJ, Seed PT, O' Sullivan G. *An Evaluation of Isotonic "Sport Drinks" During Labor*. Anesth Analg. 2002, 94(2):404-408. O'Sullivan G, Liu B, Hart D, Seed P, Shennan A. *Effect of food intake during labour on obstetric outcome: randomised controlled trial.* BMJ 2009, 24;338:b784. Scheepers HC, Thans MC, de Jong PA, Essed GG, Le Cessie S, Kanhai HH. *A double-blind, randomised, placebo controlled study on the influence of carbohydrate solution intake during labour.* BJOG 2002, 109(2):178-81. Scrutton MJ, Metcalfe GA, Lowy C, Seed PT, O'Sullivan G. Eating in labour. *A randomised controlled trial assessing the risks and benefits*. Anaesthesia. 1999, 54(4):329-34. Tranmer JE, Hodnett ED, Hannah ME, Stevens BJ. *The effect of unrestricted oral carbohydrate intake on labor progress*. J Obstet Gynecol Neonatal Nurs. 2005, 34(3):319-28. **Systematic reviews** Singata M, Tranmer J, Gyte GM. *Restricting oral fluid and food intake during labour.* Cochrane Database Syst Rev. 2013 Aug 22;8:CD003930.

Pregnancy and delivery – Relaxation techniques (First Aid)

Question (PICO)	In women (P), are relaxation techniques (I) compared to usual care (C) effective for maternal or foetal/neonatal outcomes during labour (O)?
Search Strategy	The starting point for this PICO was the NICE guideline 2014 entitled 'Intrapartum care: care of healthy women and their babies during childbirth'. This guideline includes a Cochrane systematic review of 2011 (Smith, 2011, Australia) which addressed this PICO question and was used as source of individual studies. Therefore, no search strategies regarding additional experimental studies (i.e. randomized controlled trials) were performed since the Cochrane systematic review will be updated every 5 years.

	Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	07 July 2015
In/Exclusion criteria	**Population:** Include: women in labour. **Intervention:** Include: Relaxation techniques (yoga, music, audio) **Comparison:** Include: placebo, no treatment, usual care Exclude: other methods of pain management (hypnosis, biofeedback, intracutaneous or subcutaneous water injection, immersion in water, aromatherapy, relaxation techniques (yoga, music, audio) or acupuncture or acupressure or psychoprophylaxis. **Outcome:** Include: Pain and other direct health-related outcomes **Study design:** Include: a systematic review was included if the search strategy and selection criteria are clearly described and if at least MEDLINE and one other relevant database was searched. If no systematic review was published within the last 5 years, individual experimental and/or observational studies were included. Exclude: case series**,** animal studies, *ex vivo* or *in vitro* studies. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline)

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Smith, 2011, Australia	Cochrane systematic review	11 studies including 1374 women	Intervention: relaxation techniques (music, yoga, audio) Control: usual care, psychoprophylaxis or other dose of relaxation technique (e.g. audio)	
Almeida, 2005, Brazil	Experimental: randomized controlled trial	65 women (primiparous) with normal labour and at low risk, in latent phase (≤4 cm dilation) of labour on admission, no obstetric disease or complications, not having previously participated in psychoprophylactic preparation courses for childbirth	Intervention: breathing techniques during contractions at different stages of labour Control: routine nursing care	Cited in SR Smith 2011
Bergstrom, 2009, Sweden		1087 nulliparous women and 1064 partners attending any of the participating clinics	Intervention: relaxation: In each session, 30 minutes were spent on practical training in breathing, relaxation and massage techniques. Psychoprophylactic training between sessions was encouraged and a booklet to facilitate homework was distributed. Control: usual care	
Chuntharapat, 2008, Thailand		74 primiparous women without serious illness or high-risk complications during pregnancy;	Intervention: yoga: a series of 6 60-minute yoga practice sessions at the 26th, 28th,	

		receiving antenatal care from the start, or at least 2nd trimester of pregnancy; and, without prior experience of practising yoga; >18 years old	30th, 32nd, 34th, 36th, and 37th week of gestation Control: usual care	
Liu, 2010, Taiwan		103 primiparous women, planned vaginal delivery, singleton; no intention to use pharmacological analgesic during labour	Intervention: relaxation: listening for 30 minutes during the latent/active phase of labour to classical/light/popular/crystal children's/Chinese religious music Control: usual care	
Yildirim, 2004, Turkey	Experimental: randomized controlled trial	40 primiparous women, 38-42 weeks pregnant, at low risk, expecting normal vaginal delivery	Intervention: relaxation: nurse/self-administered massage, breathing exercises, position changes to relax, Control: usual care	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Pain intensity (latent phase)	Relaxation vs usual care	Statistically significant: 1.75±0.71 vs 3±1.48 MD: -1.25, 95%CI [-1.97;-0.53] (p=0.00066) *In favour of relaxation*	1, 20 vs 20 §	Yildirim, 2004
Pain intensity (active phase)		Statistically significant: 5.8±1.15 vs 8.35±1.08 MD: -2.55, 95%CI [-3.24;-1.86] (p<0.00001) *In favour of relaxation*		
Satisfaction with pain relief in labour		Statistically significant: 8/20 vs 1/20 RR: 8.00, 95%CI [1.10;58.19] (p=0.040) *In favour of relaxation*		
Maternal perception of pain		Not statistically significant: 4.53±1.66 vs 4.53±1.66 MD: 0, 95%CI [-0.22;0.22] (p=1.00)	1, 448 vs 456	Bergstrom, 2009
Satisfaction with childbirth experience		Not statistically significant: 45.9±24 vs 46.3±23.1 MD: -0.40, 95%CI [-3.47;2.67] (p=0.80) ¥		
Use of pharmacological pain relief (epidural)		Not statistically significant: 228/448 vs 233/456 RR: 1.00, 95%CI [0.88;1.13] (p=0.95)		
Length of labour		Not statistically significant: 445±158 vs 340±168 MD: 105, 95%CI [-1.50;213] (p=0.053) ¥	1, 19 vs 17 §	Almeida, 2005

Pain intensity (latent phase)	Yoga vs usual care	Statistically significant: 51.79±10.46 vs 57.91±12.83 MD: -6.12, 95%CI [-11.77;-0.47] (p=0.034) *In favour of yoga*	1, 33 vs 33 §	Chuntharapat, 2008
Satisfaction with pain relief in labour (latent phase)		Statistically significant: 52.88±13.57 vs 45±12.84 MD: 7.88, 95%CI [1.51;14.25] (p=0.015) *In favour of yoga*		
Satisfaction with childbirth experience		Statistically significant: 156.7±13.43 vs 150.36±11.7 MD: 6.34, 95%CI [0.26;12.42] (p=0.041) *In favour of yoga*		
Use of pharmacological pain relief		Not statistically significant: 14/33 vs 17/33 RR: 0.82, 95%CI [0.49;1.38] (p=0.46) ¥		
Length of labour		Statistically significant: 519.88±185.68 vs 659.79±272.79 MD: -139.91, 95%CI [-252.50;-27.32] (p=0.015) *In favour of yoga*		
Augmentation with oxytocin		Not statistically significant: 13/33 vs 17/33 RR: 0.76, 95%CI [0.45;1.31] (p=0.33) ¥		
Pain intensity (latent phase)	Music versus usual care	Not statistically significant: 6.43±2.57 vs 6.6±2.34 MD: -0.17, 95%CI [-1.41;1.07] (p=0.79) ¥	1, 30 vs 30 §	Liu, 2010
Pain intensity (active phase)		Not statistically significant: 9.17±1.02 vs 9.35±1.02 MD: -0.18, 95%CI [-0.70;0.34] (p=0.49)		
Caesarean section		Not statistically significant: 5/30 vs 4/30 RR: 1.25, 95%CI [0.37;4.21] (p=0.72) ¥		
Use of pharmacological pain relief (epidural)		Not statistically significant: 15/30 vs 18/30 RR: 0.83, 95%CI [0.53;1.32] (p=0.44) ¥		
Length of labour (second stage)		Not statistically significant: 26.53±13.32 vs 29.13±21.27 MD: -2.60, 95%CI [-11.58;6.38] (p=0.57)		
Anxiety (latent phase)		Not statistically significant: 6.38±2.98 vs 5.2±2.15 MD: 1.18, 95%CI [-0.13;2.49] (p=0.079)		
Anxiety (active phase)		Not statistically significant: 8.22±2.26 vs 7.68±2.1 MD: 0.54, 95%CI [-0.56;1.64] (p=0.34)		

Mean ± SD (unless otherwise indicated)

§ Imprecision (limited sample size)
¥ Imprecision (large variability of results)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Almeida, 2005	No	Yes	No	Unclear	No
Bergstrom, 2009	No	Yes	No	No	No
Chuntharapat, 2008	Unclear	Yes	Unclear	Unclear	No
Liu, 2010	No	Yes	Yes	Unclear	No
Yilidirim, 2004	Unclear	Unclear	No	Unclear	No

Level of evidence

Relaxation versus usual care	**Initial grading High [A]**	Downgrading due to
Limitations of study design	-1	See 'Quality of evidence'
Imprecision	-1	Limited sample size
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Low [C]**	

Yoga versus usual care	**Initial grading High [A]**	Downgrading due to
Limitations of study design	-1	See 'Quality of evidence'
Imprecision	-1	
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Music versus usual care	**Initial grading High [A]**	Downgrading due to
Limitations of study design	-1	See 'Quality of evidence'
Imprecision	-1	Limited sample size
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	**Relaxation versus usual care** There is limited evidence in favour of relaxation. In making this evidence conclusion, we place a higher value on statistically significant outcomes over non-statistically significant outcomes. It was shown that relaxation resulted in a statistically significant decreased pain intensity (latent/active phase) and an increased satisfaction with pain relief, compared to usual care (Yildirim, 2004). However, a statistically significant difference in maternal perception of pain, satisfaction with childbirth experience, use of pharmacological pain relief (epidural) and length of labour, using relaxation compared to usual care, could not be demonstrated (Bergstrom, 2009 and Almeida, 2005). Evidence is of low quality and results are imprecise due to limited sample size. **Yoga versus usual care** There is limited evidence in favour of yoga. In making this evidence conclusion, we place a higher value on statistically significant outcomes over non-statistically significant outcomes. It was shown that yoga resulted in a statistically significant decreased pain intensity (latent phase), decreased length of labour and an increased satisfaction with pain relief (latent phase) and increased satisfaction with childbirth experience, compared to usual care

	(Chuntharapat, 2008). However, a statistically significant difference in use of pharmacological pain relief and augmentation with oxytocin, using yoga compared to usual care, could not be demonstrated (Chuntharapat, 2008). Evidence is of low quality and results are imprecise due to limited sample size. **Music versus usual care** There is limited evidence neither in favour of music nor usual care. A statistically significant difference in pain intensity (latent/active phase), caesarean section, use of pharmacological pain relief (epidural), length of labour (second stage) and anxiety (latent/active phase), using music compared to usual care, could not be demonstrated (Liu, 2010). Evidence is of low quality and results are imprecise due to limited sample size.
Reference(s)	**Articles** Almeida NA, De Sousa JT, Bachion MM, Silveira NA. *The use of respiration and relaxation techniques for pain and anxiety relief in the parturition process*. Revista Latino-Americana de Enfermagem 2005, 13(1):52–58. Bergstrom M, Kieler H, Waldenstrom U. *Effects of natural childbirth preparation versus standard antenatal education on epidural rates, experience of childbirth and parental stress in mothers and fathers: a randomised controlled multicentre trial*. BJOG 2009, 116(9):1167–1176. Chuntharapat S, Petpichetchian W, Hatthakit U. Yoga during pregnancy: effects on maternal comfort, labor pain and birth outcomes. Complementary Therapies in Clinical Practice 2008, 14(2):105–115. Liu YH, Chang MY, Chen CH. *Effects of music therapy on labour pain and anxiety in Taiwanese first time mothers*. Journal of Clinical Nursing 2010, 19(7-8):1065–1072. Yildirim G, Sahin NH. *The effect of breathing and skin stimulation on labour pain perception of Turkish women*. Pain Research & Management 2004, 9(4):183–187. **Systematic review** Smith CA, Levett KM, Collins CT, Crowther CA. *Relaxation techniques for pain management in labour*. Cochrane Database Syst Rev. 2011, 12:CD009514. **Guideline** NICE guideline. National Collaborating Centre for Women's and Children's Health (UK) 2014. Intrapartum Care: Care of Healthy Women and Their Babies During Childbirth.

Pregnancy and delivery – Warm compresses (First Aid)

Question (PICO)	In women (P), is the application of warm compresses (I) compared to usual care (C) effective for pain or other health-related outcomes during labour (C)?
Search Strategy	The starting point for this PICO was the NICE guideline 2007 entitled 'Intrapartum care: care of healthy women and their babies during childbirth'. This guideline included one observational study (Albers 1996) which addressed this PICO question and was used as source of individual studies. Therefore, the search strategies below aimed to find additional experimental/observational studies from 01/01/2007 until 10/07/2015. Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh Labor, Obstetric/adverse effects] OR [mh Labor, Obstetric/mortality] OR [mh Labor, Obstetric/physiology] OR [mh Labor, Obstetric/physiopathology] OR [mh Labor, Obstetric/prevention and control] OR [mh Labor, Obstetric/therapeutic use] OR [mh Labor, Obstetric/therapy] OR labor:ti,ab,kw OR labour:ti,ab,kw OR [mh Parturition/adverse effects] OR [mh Parturition/injuries] OR [mh Parturition/mortality] OR [mh Parturition/physiology] OR [mh

	Parturition/psychology] OR [mh Parturition/rehabilitation] OR [mh Parturition/therapeutic use] OR [mh Parturition/therapy] OR parturition:ti,ab,kw 2. 'compress':ti,ab,kw OR 'compresses':ti,ab,kw 3. 1-2 AND Filter: 2007-2015 **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Labor, Obstetric/adverse effects"[Mesh] OR "Labor, Obstetric/mortality"[Mesh] OR "Labor, Obstetric/physiology"[Mesh] OR "Labor, Obstetric/physiopathology"[Mesh] OR "Labor, Obstetric/prevention and control"[Mesh] OR "Labor, Obstetric/therapeutic use"[Mesh] OR "Labor, Obstetric/therapy"[Mesh] OR "labor"[TIAB] OR "labour"[TIAB] OR "Parturition/adverse effects"[Mesh] OR "Parturition/injuries"[Mesh] OR "Parturition/mortality"[Mesh] OR "Parturition/physiology"[Mesh] OR "Parturition/psychology"[Mesh] OR "Parturition/rehabilitation"[Mesh] OR "Parturition/therapeutic use"[Mesh] OR "Parturition/therapy"[Mesh] OR parturition[TIAB] 2. "compress"[TIAB] OR "compresses"[TIAB] 3. 1-2 AND Filter: 2007-2015 **Embase** (via Embase.com interface) using the following search strategy: 1. 'labor'/exp OR 'birth'/exp OR 'labor':ab,ti OR 'labour':ab,ti OR 'birth':ab,ti 2. 'compress':ab,ti OR 'compresses':ab,ti 3. 1-3 AND Filter: 2007-2015 Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	10 July 2015
In/Exclusion criteria	**Population:** Include: women in labour. **Intervention:** Include: Warm compresses **Comparison:** Include: placebo, no treatment, usual care **Outcome:** Include: Pain and other direct health-related outcomes **Study design:** Include: a systematic review was included if the search strategy and selection criteria are clearly described and if at least MEDLINE and one other relevant database was searched. If no systematic review was published within the last 5 years, individual experimental and/or observational studies were included. Exclude: case series**,** animal studies, *ex vivo* or *in vitro* studies. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline)

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Aasheim, 2011, Norway	Cochrane systematic review	8 randomized controlled trials involving 11.651 pregnant women planning to have a spontaneous vaginal birth (after 36 weeks of pregnancy, pregnant with single foetus, cephalic presentation).	Intervention: Any perineal techniques for example: perineal massage, flexion technique, Ritgen's manoeuvre, warm compresses, hands-on or hands-poised, etc., all performed during the second stage of labour Control: usual care or no intervention	

Albers, 2005, USA	Experimental: randomized controlled trial	1211 women in midwifery care, 18 years or older, healthy, expecting a vaginal birth, no medical complications, a singleton vertex presentation at term.	Intervention: Warm compresses were held continuously to the mother's perineum and external genitalia by the midwife's gloved hand during and between pushes, regardless of mother's position Control: No touch the woman's perineum until crowning of the infant's head	Cited in SR Aasheim 2011
Dahlen, 2007, Australia	Experimental: randomized controlled trial	717 nulliparous women, at least 36 weeks' pregnant, singleton pregnancy with a cephalic presentation; anticipated a normal birth, who had not performed perineal massage antenatally and were older than 16 years.	Intervention: warm packs/pads on the perineum as the baby's had begun to distend the perineum and the woman was aware of a stretching sensation. A sterile pad was soaked in a metal jug with boiled tap water (between 45 and 59 degrees C) then wrung out and gently placed on the perineum during contractions. The pad was re-soaked to maintain warmth between contractions. The water in the jug was replaced every 15 min until delivery. Control: standard group which did not have warm pack applied to their perineum in second stage	Cited in SR Aasheim 2011

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
3rd or 4th degree tears	Warm compresses vs hands off/no warm compresses	Statistically significant: 18/764 vs 37/761 RR: 0.48, 95%CI [0.28;0.84] (p=0.0094) *In favour of warm compresses*	2, 764 vs 761	Albers 2005, Dahlen 2007
Episotomy		Not statistically significant: 40/764 vs 43/761 § RR: 0.93, 95%CI [0.62;1.39] (p=0.71) ¥		
Intact perineum		Not statistically significant: 171/764 vs 163/761 § RR: 1.05, 95%CI [0.86;1.26] (p=0.65)		

§ Imprecision (limited sample size)

¥ Imprecision (large variability of results)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Albers, 2005	No	Yes	No	No	No
Dahlen, 2007	No	Yes	No	Unclear	No

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See 'Quality of evidence'
Imprecision	-1	Limited sample size
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Moderate [B]**	

Conclusion	There is limited evidence in favour of warm compresses. In making this evidence conclusion, we place a higher value on statistically significant outcomes over non-statistically significant outcomes. It was shown that warm compresses resulted in a statistically significant decreased risk of 3rd/4th degree tears (Albers, 2005 and Dahlen, 2007) compared to control (hands off/no warm compresses). However, a statistically significant difference in episotomy and intact perineum could not be demonstrated (Albers, 2005 and Dahlen, 2007). Evidence is of moderate quality and results cannot be considered precise due to the low number of events.
Reference(s)	**Articles** Albers LL, Sedler KD, Bedrick EJ, Teaf D, Peralta P. *Midwifery care measures in the second stage of labor and reduction of genital tract trauma at birth: a randomized trial.* Journal of Midwifery & Women's Health 2005, 50(5):365–372. Dahlen HG, Homer CS, Cooke M, Upton AM, Nunn R, Brodrick B. *Perineal outcomes and maternal comfort related to the application of perineal warm packs in the second stage of labor: a randomized controlled trial.* Birth 2007, 34(4):282–290. **Systematic reviews** Aasheim V, Nilsen ABV, Lukasse M, Reinar LM. *Perineal techniques during the second stage of labour for reducing perineal trauma.* Cochrane Database Syst Rev. 2011, 12:CD006672. **Guideline** NICE guideline. National Collaborating Centre for Women's and Children's Health (UK) 2007. Intrapartum Care: Care of Healthy Women and Their Babies During Childbirth.

Emergency childbirth – Involving the birth companion during labour (First Aid)

Question (PICO)	In pregnant women in labour (P), does involving a birth companion(s) (I), compared to not involving a birth companion(s) (C), influence the delivery (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "labor, obstetric"] OR [mh "parturition"] OR ((labor:ti,ab,kw OR labour:ti,ab,kw) AND [mh "female"]) OR parturition*:ti,ab,kw OR childbirth*:ti,ab,kw OR [mh "delivery, obstetric"] OR (obstetric NEXT/1 deliver*):ti,ab,kw OR [mh "perinatal care"] OR (perinatal NEXT/1 care):ti,ab,kw 2. (birth NEXT/1 compan*):ti,ab,kw OR [mh "spouses"] OR husband*:ti,ab,kw OR spouse*:ti,ab,kw OR [mh "social support"] OR social support:ti,ab,kw 3. 1-2 AND Cochrane systematic review identified: Hodnett, 2013

Search date	12th May 2016
In/Exclusion criteria	**Population:** Include: Pregnant women in labour **Intervention:** Include: Continuous support of the pregnant woman by a birth companion. Exclude: Support of the pregnant woman by hospital staff, doula or other professional. Support that was not continuous during labour. **Comparison:** Include: Standard care without continuous support **Outcome:** Include: Outcomes concerning course of the delivery, maternal and neonatal wellbeing and maternal experiences. **Study design:** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: observational studies if intervention is already included in experimental studies, case series, cross-sectional studies, animal studies, ex vivo or in vitro studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language:** Include: English, French, German, Dutch. **Publication year**: Include: all years.

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison/Risk factor	Remarks
Hodnett, 2013, Canada	Cochrane systematic review	22 clinical trials, consisting of 15288 women in labour.	Continuous presence and support for the pregnant woman during the period of labour, provided by either hospital personnel, a doula or companion chosen by the pregnant woman and compared to standard hospital care, which could consist of other interventions, such as epidural analgesia, but did not include continuous presence and support. [As our PICO question specifically concerns a birth companion, only outcomes analysed in the subgroup analysis involving specifically this group was extracted]	Assessed as up to date: 29/06/2013

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Use of any analgesia/anaesthesia	Continuous support vs standard care	Statistically significant: 372/704 vs 405/704 RR: 0.94, 95%CI [0.88;1.00] (p=0.045) *In favour of continuous support*	4, 704 vs 704	Hodnett, 2013
Use of synthetic oxytocin during labour		Not statistically significant: 483/1017 vs 514/1024 RR: 0.99, 95%CI [0.96;1.01] (p=0.32)	6, 1017 vs 1024	
Spontaneous vaginal birth		Statistically significant: 736/923 vs 734/1012	5, 923 vs 1012	

		RR: 1.12, 95%CI [1.07;1.17] (p<0.00001) *In favour of continuous support*		
Caesarean birth		Not statistically significant: 160/1029 vs 200/1030 § RR: 0.83, 95%CI [0.69;1.01] ¥ (p=0.062)	6, 1029 vs 1030	
Admission to special care nursery		Not statistically significant: 17/320 vs 12/320 § RR: 1.40, 95%CI [0,67;2.93] ¥ (p=0.37)	2, 320 vs 320	
Negative rating/feelings about birth experience		Statistically significant: 245/833 vs 453/833 RR: 0.57, 95%CI [0.51;0.64] (p<0.00001) *In favour of continuous support*	4, 833 vs 875	

¥ Imprecision (large variability of results)
§ Imprecision (low number of events)

Quality of evidence

	High [A]	Downgrading due to
Limitations of study design	0	See Hodnett, 2013
Imprecision	0	
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**High [A]**	

Conclusion	There is evidence in favour of continuous support by a birth companion. In making this evidence conclusion, we place a higher value on use of analgesia/anaesthesia, spontaneous vaginal birth and negative rating/feelings about birth experience over use of synthetic oxytocin, caesarian birth and admission to special care nursery. It was shown that continuous support resulted in a statistically significant decrease of the use of analgesia/anaesthesia and the occurrence of negative ratings/feelings about the birth experience and an increase in the amount of spontaneous vaginal births, compared to standard care. Evidence is of high quality. In contrast, it was shown that continuous support did not result in a statistically significant difference in use of synthetic oxytocin, compared to standard care. Evidence is of high quality. Furthermore, a statistically significant decrease of caesarean birth or admission to special care nursery, using continuous support compared to standard care, could not be demonstrated. Evidence is of moderate quality.
Reference(s)	**Systematic reviews** Hodnett ED, Gates S, Hofmeyr GJ, Sakala C. *Continuous support for women during childbirth.* Cochrane Database Syst Rev. 2013 Jul 15;7:CD003766.

Emergency childbirth – Involving the birth companion during labour (First Aid)

Question (PICO)	In pregnant women in labour (P), does involving a birth companion(s) (I), compared to not involving a birth companion(s) (C), influence the delivery (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "labor, obstetric"] OR [mh "parturition"] OR ((labor:ti,ab,kw OR labour:ti,ab,kw) AND [mh "female"]) OR parturition*:ti,ab,kw OR childbirth*:ti,ab,kw OR [mh "delivery, obstetric"] OR (obstetric NEXT/1 deliver*):ti,ab,kw OR [mh "perinatal care"] OR (perinatal NEXT/1 care):ti,ab,kw 2. (birth NEXT/1 compan*):ti,ab,kw OR [mh "spouses"] OR husband*:ti,ab,kw OR spouse*:ti,ab,kw OR [mh "social support"] OR social support:ti,ab,kw 3. 1-2 AND Cochrane systematic review identified: Hodnett, 2013
Search date	12th May 2016
In/Exclusion criteria	**Population:** Include: Pregnant women in labour **Intervention:** Include: Continuous support of the pregnant woman by a birth companion. Exclude: Support of the pregnant woman by hospital staff, doula or other professional. Support that was not continuous during labour. **Comparison:** Include: Standard care without continuous support **Outcome:** Include: Outcomes concerning course of the delivery, maternal and neonatal wellbeing and maternal experiences. **Study design:** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: observational studies if intervention is already included in experimental studies, case series, cross-sectional studies, animal studies, ex vivo or in vitro studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English, French, German, Dutch. **Publication year**: Include: all years.

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison/Risk factor	Remarks
Hodnett, 2013, Canada	Cochrane systematic review	22 clinical trials, consisting of 15288 women in labour.	Continuous presence and support for the pregnant woman during the period of labour, provided by either hospital personnel, a doula or companion chosen by the pregnant woman and compared to standard hospital care, which could consist of other interventions, such as epidural analgesia, but did not include continuous presence and support. [As our PICO question specifically concerns a birth companion, only outcomes analysed in the subgroup analysis involving specifically this group was extracted]	Assessed as up to date: 29/06/2013

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Use of any analgesia/anaesthesia	Continuous support vs standard care	Statistically significant: 372/704 vs 405/704 RR: 0.94, 95%CI [0.88;1.00] (p=0.045) *In favour of continuous support*	4, 704 vs 704	Hodnett, 2013
Use of synthetic oxytocin during labour		Not statistically significant: 483/1017 vs 514/1024 RR: 0.99, 95%CI [0.96;1.01] (p=0.32)	6, 1017 vs 1024	
Spontaneous vaginal birth		Statistically significant: 736/923 vs 734/1012 RR: 1.12, 95%CI [1.07;1.17] (p<0.00001) *In favour of continuous support*	5, 923 vs 1012	
Caesarean birth		Not statistically significant: 160/1029 vs 200/1030 § RR: 0.83, 95%CI [0.69;1.01] ¥ (p=0.062)	6, 1029 vs 1030	
Admission to special care nursery		Not statistically significant: 17/320 vs 12/320 § RR: 1.40, 95%CI [0,67;2.93] ¥ (p=0.37)	2, 320 vs 320	
Negative rating/feelings about birth experience		Statistically significant: 245/833 vs 453/833 RR: 0.57, 95%CI [0.51;0.64] (p<0.00001) *In favour of continuous support*	4, 833 vs 875	

¥ Imprecision (large variability of results)

§ Imprecision (low number of events)

Quality of evidence

	High [A]	Downgrading due to
Limitations of study design	0	See Hodnett, 2013
Imprecision	0	
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**High [A]**	

Conclusion	There is evidence in favour of continuous support by a birth companion. In making this evidence conclusion, we place a higher value on use of analgesia/anaesthesia, spontaneous vaginal birth and negative rating/feelings about birth experience over use of synthetic oxytocin, caesarian birth and admission to special care nursery. It was shown that continuous support resulted in a statistically significant decrease of the use of analgesia/anaesthesia and the occurrence of negative ratings/feelings about the birth experience and an increase in the amount of spontaneous vaginal births, compared to standard care. Evidence is of high quality. In contrast, it was shown that continuous support did not result in a statistically significant difference in use of synthetic oxytocin, compared to standard care. Evidence is of high quality. Furthermore, a statistically significant decrease of caesarean birth or admission to special care nursery, using continuous support compared to standard care, could not be demonstrated. Evidence is of moderate quality.
Reference(s)	**Systematic reviews** Hodnett ED, Gates S, Hofmeyr GJ, Sakala C. *Continuous support for women during childbirth.* Cochrane Database Syst Rev. 2013 Jul 15;7:CD003766.

Uterine massage for postpartum haemorrhage (First Aid)

Question (PICO)	In mothers that bleed heavily after delivery (P), does massaging the belly (I), compared to not massaging the belly (C), influence post-partum haemorrhage (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "postpartum hemorrhage"] OR [mh "uterine hemorrhage"] OR (postpartum NEXT/1 hemorrhag*):ti,ab,kw OR (postpartum NEXT/1 haemorrhag*):ti,ab,kw OR (obstetric NEXT/1 hemorrhag*):ti,ab,kw OR (obstetric NEXT/1 heamorrhag*):ti,ab,kw OR (uterine NEXT/1 hemorrhag*):ti,ab,kw OR (uterine NEXT/1 haemorrhag*):ti,ab,kw OR (postpartum NEXT/1 bleed*):ti,ab,kw OR (obstetric NEXT/1 bleed*):ti,ab,kw OR (uterine NEXT/1 bleed*):ti,ab,kw 2. [mh "massage"] OR massag*:ti,ab,kw OR [mh ^"musculoskeletal manipulations"] OR (manual NEXT/1 therap*):ti,ab,kw OR (musculoskeletal NEXT/1 manipul*):ti,ab,kw OR (manip* NEXT/1 therap*):ti,ab,kw 3. 1-2 AND Cochrane systematic review identified: Hofmeyr, 2013
Search date	13th May 2016

In/Exclusion criteria	**Population:** Include: Pregnant women with postpartum haemorrhage **Intervention:** Include: Uterine massage **Comparison:** Include: Any other intervention/no intervention **Outcome:** Include: Outcomes concerning functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of the symptoms. **Study design:** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: observational studies if intervention is already included in experimental studies, case series, cross-sectional studies, animal studies, ex vivo or in vitro studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English, French, German, Dutch. **Publication year**: Include: all years.

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison/Risk factor	Remarks
Hofmeyr, 2013, South Africa	Cochrane systematic review	2 randomised controlled trials, including 200 and 1964 women in labour (the second trial was performed in two sites with significant heterogeneity between sites, and was therefore analysed as 2 studies by the authors of the SR)	Uterine massage during the third stage of labour, started after birth, and either before or after placental delivery, compared to no intervention, a mock intervention or an alternative intervention, with or without other third stage co-interventions.	Assessed as up to date: 9th Sept 2011, but published in issue 7, 2013 [For the outcome "Late placenta delivery", there is an error in the Cochrane review, therefore data from the original study (Abdel-Aleem, 2010) was extracted]

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Blood loss of 500 mL or more	Uterine massage started before placental delivery with oxytocin 10U vs oxytocin 10U	Not statistically significant: 41/652 vs 22/639 § RR: 1.56, 95%CI [0.44;5.49] ¥ (p=0.49)	2, 652 vs 639	Hofmeyr, 2013
	Uterine massage started after placental delivery with	Not statistically significant: 4/98 vs 8/102 §	1, 98 vs 102	

	oxytocin 10U vs oxytocin 10U	RR: 0.52, 95%CI [0.16;1.67] ¥ (p=0.27)		
	Uterine massage started before or after placental delivery with oxytocin 10U vs oxytocin 10U	Not statistically significant: 45/750 vs 30/741 § RR: 1.14, 95%CI [0.39;3.32] ¥ (p=0.81)	3, 750 vs 741	
Blood loss of 1000 mL or more	Uterine massage started before placental delivery with oxytocin 10U vs oxytocin 10U	Not statistically significant: 3/652 vs 1/639 § RR: 2.96, 95%CI [0.31;28.35] ¥ (p=0.35)	2, 652 vs 639	
Mean blood loss, 30 min after trial entry (ml)	Uterine massage started after placental delivery with oxytocin 10U vs oxytocin 10U	Statistically significant: 168.8±90.5 vs 210.4±146.2 MD: -41.60, 95%CI [-75.16;-8.04] (p=0.015) *In favour of uterine massage*	2, 98 vs 102 §	
Mean blood loss, 60 min after trial entry (ml)		Statistically significant: 204.3±121.4 vs 281.7±173.1 MD: -77.40, 95%CI [-118.71;-36.09] (p=0.00024) *In favour of uterine massage*		
Blood haemoglobin < 8 g/dL	Uterine massage started before placental delivery with oxytocin 10U vs oxytocin 10U	Not statistically significant: 5/191 vs 85/191 § RR: 0.63, 95%CI [0.21;1.88] ¥ (p=0.40)	1, 191 vs 191	
Late placenta delivery (>30 min after birth)	Uterine massage started before placental delivery with oxytocin 10U vs oxytocin 10U	Not statistically significant: 9/655 vs 11/634 § RR: 0.79, 95%CI [0.33;1.88] * ¥ (p=0.60)	2, 655 vs 634	
	Uterine massage started after placental delivery with oxytocin 10U vs oxytocin 10U	Not estimable: 0/98 vs 0/102 §	1, 98 vs 102	
	Uterine massage started before or after placental delivery with oxytocin 10U vs oxytocin 10U	Not statistically significant: 9/753 vs 11/736 § RR: 0.80, 95%CI [0.33;1.92] * ¥ (p=0.62)	3, 753 vs 736	
Need for manual removal of the placenta	Uterine massage started before placental delivery with oxytocin 10U vs oxytocin 10U	Not statistically significant: 13/655 vs 11/634 § RR: 1.77, 95%CI [0.18;17.62] ¥ (p=0.63)	2, 655 vs 634	
Use of additional uterotonics	Uterine massage started before placental delivery with oxytocin 10U vs oxytocin 10U	Not statistically significant: 21/638 vs 20/622 § RR: 1.02, 95%CI [0.56;1.85] ¥ (p=0.95)	2, 638 vs 622	
	Uterine massage started after placental delivery with oxytocin 10U vs oxytocin 10U	Statistically significant: 5/98 vs 26/102 § RR: 0.20, 95%CI [0.08;0.50] (p=0.00058) *In favour of uterine massage*	1, 98 vs 102	
	Uterine massage started before or after placental	Not statistically significant: 26/736 vs 46/724 §	3, 736 vs 724	

	delivery with oxytocin 10U vs oxytocin 10U	RR: 0.52, 95%CI [0.15;1.81] ¥ (p=0.30)		
Need for blood transfusion	Uterine massage started before placental delivery with oxytocin 10U vs oxytocin 10U	Not statistically significant: 4/637 vs 4/620 § RR: 0.97, 95%CI [0.26;3.58] ¥ (p=0.97)	2, 637 vs 620	
	Uterine massage started after placental delivery with oxytocin 10U vs oxytocin 10U	Not estimable: 0/98 vs 0/102	1, 98 vs 102	
	Uterine massage started before or after placental delivery with oxytocin 10U vs oxytocin 10U	Not statistically significant: 4/735 vs 4/722 § RR: 0.97, 95%CI [026;3.58] ¥ (p=0.97)	1, 735 vs 722	
Maternal death or severity morbidity	Uterine massage started after placental delivery with oxytocin 10U vs oxytocin 10U	Not estimable: 0/98 vs 0/102	1, 98 vs 102	

Mean ± SD (unless otherwise indicated)
¥ Imprecision (large variability of results)
§ Imprecision (low number of events)

Quality of evidence

	High [A]	Downgrading due to
Limitations of study design	0	See Hofmeyr, 2013
Imprecision	-1	Low numbers of events, sample sizes and large variability of the results
Inconsistency	-1	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Low [C]**	

Conclusion	There is limited evidence neither in favour of uterine massage with 10U oxytocin nor 10U oxytocin: In making this evidence conclusion, we place a higher value on the amount of patients with >500 mL blood loss over a decrease in mean blood loss, and we place a higher value on the bigger studies, which could not demonstrate an effect. It was shown that uterine massage with 10U oxytocin resulted in a statistically significant decrease of mean blood loss, 30 and 60 min after trial entry, compared to 10U oxytocin. In contrast, a statistically significant decreased risk of > 500 mL blood loss, > 1000 mL blood loss, blood haemoglobin <8 mg/dL, late placenta delivery, manual placenta removal, use of additional uterotonics, the need for blood transfusion and maternal death or severe morbidity using uterine massage with 10U oxytocin compared to 10U oxytocin could not be demonstrated. Evidence is of low quality and results of these studies are imprecise due to limited sample sizes, low numbers of events and large variability of results.
Reference(s)	**Systematic reviews** Hofmeyr GJ, Abdel-Aleem H, Abdel-Aleem MA. *Uterine massage for preventing postpartum haemorrhage.* Cochrane Database Syst Rev. 2013 Jul 1;7:CD006431.

Urinating for postpartum haemorrage (First Aid)

Question (PICO)	In mothers that bleed heavily after delivery (P), does encouraging the women to urinate (I), compared to not encouraging the women to urinate (C), influence post-partum haemorrhage (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "postpartum hemorrhage"] OR [mh "uterine hemorrhage"] OR (postpartum NEXT/1 hemorrhag*):ti,ab,kw OR (postpartum NEXT/1 haemorrhag*):ti,ab,kw OR (obstetric NEXT/1 hemorrhag*):ti,ab,kw OR (obstetric NEXT/1 haemorrhag*):ti,ab,kw OR (uterine NEXT/1 hemorrhag*):ti,ab,kw OR (uterine NEXT/1 haemorrhag*):ti,ab,kw OR (postpartum NEXT/1 bleed*):ti,ab,kw OR (obstetric NEXT/1 bleed*):ti,ab,kw OR (uterine NEXT/1 bleed*):ti,ab,kw OR (uterus NEXT/1 bleed*):ti,ab,kw OR (uterus NEXT/1 hemorrhag*):ti,ab,kw OR (uterus NEXT/1 haemorrhag*):ti,ab,kw 2. [mh "urination"] OR urinat*:ti,ab,kw OR mict*:ti,ab,kw OR void*:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for guidelines, systematic reviews, experimental and observational studies using the following search strategy: 1. "postpartum hemorrhage"[MeSH] OR "uterine hemorrhage"[MeSH] OR postpartum hemorrhag*[TIAB] OR postpartum haemorrhag*[TIAB] OR obstetric hemorrhag*[TIAB] OR obstetric haemorrhag*[TIAB] OR uterine hemorrhag*[TIAB] OR uterine haemorrhag*[TIAB] OR postpartum bleed*[TIAB] OR obstetric bleed*[TIAB] OR uterine bleed*[TIAB] OR uterus bleed*[TIAB] OR uterus hemorrhag*[TIAB] OR uterus haemorrhag*[TIAB] 2. "urination"[MeSH] OR urinat*[TIAB] OR mict*[TIAB] OR void*[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'postpartum hemorrhage'/exp OR 'obstetric hemorrhage'/exp OR 'uterus bleeding'/exp OR (postpartum NEXT/1 hemorrhag*):ab,ti OR (postpartum NEXT/1 haemorrhag*):ab,ti OR (obstetric NEXT/1 hemorrhag*):ab,ti OR (obstetric NEXT/1 haemorrhag*):ab,ti OR (uterine NEXT/1 hemorrhag*):ab,ti OR (uterine NEXT/1 haemorrhag*):ab,ti OR (postpartum NEXT/1 bleed*):ab,ti OR (obstetric NEXT/1 bleed*):ab,ti OR (uterine NEXT/1 bleed*):ab,ti OR (uterus NEXT/1 bleed*) OR (uterus NEXT/1 hemorrhag*):ab,ti OR (uterus NEXT/1 heamorrhag*):ab,ti 2. 'micturition'/exp OR urinat*:ab,ti OR mict*:ab,ti OR void*:ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	13th May 2016
In/Exclusion criteria	**Population:** Include: Pregnant women with postpartum hemorrhage **Intervention:** Include: Urinating **Comparison:** Include: Any other intervention/no intervention **Outcome:** Include: Outcomes concerning functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of the symptoms.

	Study design: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: observational studies if intervention is already included in experimental studies, case series, cross-sectional studies, animal studies, ex vivo or in vitro studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English, French, German, Dutch. **Publication year**: Include: all years.

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	Not applicable

Sudden infant death syndrome (SIDS) – Position (Prevention)

Question (PICO)	In babies (P), is the supine position (I) effective to prevent sudden infant death (O), compared to the prone/side position (C)?
Search Strategy	Databases **The Cochrane Library** for systematic reviews using the following search strategy: 1. [mh sudden infant death] OR "sudden infant death":ti,ab,kw OR "SID":ti,ab,kw OR "SIDS":ti,ab,kw OR "Crib death":ti,ab,kw OR "Cot death":ti,ab,kw 2. [mh meta-analysis] OR meta analys*:ti,ab,kw OR meta-analys*:ti,ab,kw OR 'cochrane':ti,ab,kw OR 'embase':ti,ab,kw OR 'pubmed':ti,ab,kw OR 'medline':ti,ab,kw OR 'reference list':ti,ab,kw OR 'reference lists':ti,ab,kw OR 'bibliography':ti,ab,kw OR 'bibliographies':ti,ab,kw OR 'hand-search':ti,ab,kw OR 'manual search':ti,ab,kw OR 'selection criteria':ti,ab,kw OR 'relevant journals':ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for systematic reviews using the following search strategy: 1. "Sudden infant death"[Mesh] OR "sudden infant death"[TIAB] OR "SID"[TIAB] OR "SIDS"[TIAB] OR "Crib death"[TIAB] OR "Cot death"[TIAB] 2. "Guideline "[Publication Type] OR "Practice Guidelines as Topic"[Mesh] OR "Practice Guideline "[Publication Type] OR practice guideline*[TIAB] OR Meta-Analysis as Topic[Mesh] OR meta analy*[TIAB] OR metaanaly*[TIAB] OR Meta-Analysis[Publication Type] OR systematic review*[TIAB] OR systematic overview*[TIAB] OR Review Literature as Topic[Mesh] OR cochrane[TIAB] OR

	embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB] OR reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB] OR selection criteria[TIAB] OR data extraction[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) for systematic reviews using the following search strategy: 1. 'Sudden infant death'/exp OR 'sudden infant death':ab,ti OR 'SID':ab,ti OR 'SIDS':ab,ti OR "Crib death":ab,ti OR "Cot death":ab,ti 2. 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti 3. 1-2 AND **The Cochrane Library** using the following search strategy: 1. [mh sudden infant death] OR "sudden infant death":ti,ab,kw OR "SID":ti,ab,kw OR "SIDS":ti,ab,kw OR "Crib death":ti,ab,kw OR "Cot death":ti,ab,kw 2. [mh prone position] OR [mh supine position] OR 'prone position':ti,ab,kw OR 'supine position':ti,ab,kw OR 'side position':ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Sudden infant death"[Mesh] OR "sudden infant death"[TIAB] OR "SID"[TIAB] OR "SIDS"[TIAB] OR "Crib death"[TIAB] OR "Cot death"[TIAB] 2. "Prone position"[Mesh] OR "Supine position"[Mesh] OR "prone position"[TIAB] OR "supine position"[TIAB] OR "side position"[TIAB] 3. 1-2 AND Filter: 2006-2015 **Embase** (via Embase.com interface) using the following search strategy: 1. 'Sudden infant death'/exp OR 'sudden infant death':ab,ti OR 'SID':ab,ti OR 'SIDS':ab,ti OR "Crib death":ab,ti OR "Cot death":ab,ti 2. 'prone position'/exp OR 'supine position'/exp OR 'prone position':ab,ti OR 'supine position':ab,ti OR 'side position':ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	14 July 2015
In/Exclusion criteria	**Population:** Included: infants **Intervention:** Include: sleeping on their back **Comparison:** Include: sleeping on their front/side **Outcome:** Include: sudden infant death **Study design:** Include: a systematic review was included if the search strategy and selection criteria are clearly described and if at least MEDLINE and one other relevant database was searched. If no systematic review was published within the last 5 years, individual experimental and/or observational studies were included. Exclude: case series**,** animal studies, *ex vivo* or *in vitro* studies. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline)

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Gilbert, 2005, United Kingdom	Systematic review	40 observational studies (case-control and cohort studies) investigating associations between infant sleeping positions and sudden infant death syndrome	Intervention: sleeping in the supine position Control: sleeping in the prone position	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Sudden infant death syndrome	Front vs back position	Statistically significant: (Total) number of events not reported OR: 4.46, 95%CI [2.98;6.68] ($p<0.05$) *In favour of back position*	25, 1478 vs 546	Gilbert, 2005
	Side vs back position	Statistically significant: (Total) number of events not reported OR: 1.36, 95%CI [1.03;1.80] ($p<0.05$) *In favour of back position*	24, 1471 vs 537	

Quality of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	0	See systematic review Gilbert 2005
Imprecision	0	
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is limited evidence in favour of sleeping in the supine position. It was shown that sleeping in the supine position resulted in a statistically significant decreased risk of sudden infant death, compared to sleeping in the prone/side position (Gilbert 2005). Evidence is of low/very low quality.
Reference(s)	**Systematic reviews** Gilbert R, Salanti G, Harden M, See S. *Infant sleeping position and the sudden infant death syndrome: systematic review of observational studies and historical review of recommendations from 1940 to 2002*. Int J Epidemiol. 2005, 34(4):874-87.

Sudden infant death syndrome (SIDS) – Breast feeding (Prevention)

Question (PICO)	In babies (P), is breast feeding (I) compared to no breast feeding (C) effective to prevent sudden infant death syndrome (O)?
Search Strategy	Databases **The Cochrane Library** for systematic reviews using the following search strategy: 1. [mh sudden infant death] OR "sudden infant death":ti,ab,kw OR "SID":ti,ab,kw OR "SIDS":ti,ab,kw OR "Crib death":ti,ab,kw OR "Cot death":ti,ab,kw 2. [mh meta-analysis] OR meta analys*:ti,ab,kw OR meta-analys*:ti,ab,kw OR 'cochrane':ti,ab,kw OR 'embase':ti,ab,kw OR 'pubmed':ti,ab,kw OR 'medline':ti,ab,kw OR 'reference list':ti,ab,kw OR 'reference lists':ti,ab,kw OR 'bibliography':ti,ab,kw OR

	'bibliographies':ti,ab,kw OR 'hand-search':ti,ab,kw OR 'manual search':ti,ab,kw OR 'selection criteria':ti,ab,kw OR 'relevant journals':ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for systematic reviews using the following search strategy: 1. "Sudden infant death"[Mesh] OR "sudden infant death"[TIAB] OR "SID"[TIAB] OR "SIDS"[TIAB] OR "Crib death"[TIAB] OR "Cot death"[TIAB] 2. "Guideline "[Publication Type] OR "Practice Guidelines as Topic"[Mesh] OR "Practice Guideline "[Publication Type] OR practice guideline*[TIAB] OR Meta-Analysis as Topic[Mesh] OR meta analy*[TIAB] OR metaanaly*[TIAB] OR Meta-Analysis[Publication Type] OR systematic review*[TIAB] OR systematic overview*[TIAB] OR Review Literature as Topic[Mesh] OR cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB] OR reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB] OR selection criteria[TIAB] OR data extraction[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) for systematic reviews using the following search strategy: 1. 'Sudden infant death'/exp OR 'sudden infant death':ab,ti OR 'SID':ab,ti OR 'SIDS':ab,ti OR "Crib death":ab,ti OR "Cot death":ab,ti 2. 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti 3. 1-2 AND **The Cochrane Library** for controlled trials using the following search strategy: 1. [mh sudden infant death] OR "sudden infant death":ti,ab,kw OR "SID":ti,ab,kw OR "SIDS":ti,ab,kw OR "Crib death":ti,ab,kw OR "Cot death":ti,ab,kw 2. [mh breast feeding] OR "breastfeeding":ti,ab,kw OR "breast feeding":ti,ab,kw 3. 1-2 AND Filter: 2012-2015 **MEDLINE** (via PubMed interface) for individual studies using the following search strategy: 1. "Sudden infant death"[Mesh] OR "sudden infant death"[TIAB] OR "SID"[TIAB] OR "SIDS"[TIAB] OR "Crib death"[TIAB] OR "Cot death"[TIAB] 2. "Breast feeding"[Mesh] OR "breastfeeding"[TIAB] OR "breast feeding"[TIAB] 3. 1-2 AND Filter: 2012-2015 **Embase** (via Embase.com interface) for individual studies using the following search strategy: 1. 'Sudden infant death'/exp OR 'sudden infant death':ab,ti OR 'SID':ab,ti OR 'SIDS':ab,ti OR "Crib death":ab,ti OR "Cot death":ab,ti 2. 'Breast feeding'/exp OR 'breastfeeding':ab,ti OR 'breast feeding':ab,ti 3. 1-2 AND Filter: 2012-2015 Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	14 July 2015

In/Exclusion criteria	**Population:** Include: infants **Intervention:** Include: breast feeding **Comparison:** Include: no breast feeding **Outcome:** Include: sudden infant death **Study design:** Include: a systematic review was included if the search strategy and selection criteria are clearly described and if at least MEDLINE and one other relevant database was searched. If no systematic review was published within the last 5 years, individual experimental and/or observational studies were included. Exclude: case series**,** animal studies, *ex vivo* or *in vitro* studies. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline)

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Hauck, 2011, USA	Systematic review	A meta-analysis of 7 case-control studies (1988-2001) involving babies who received breast feeding (cases) or not (controls)	Intervention: any breast feeding (breastfeeding at discharge from hospital) Control: no breast feeding	6 criteria for inclusion were: (1) an appropriate definition for SIDS, (2) autopsies performed in >98% of cases, (3) an adequate description of SIDS ascertainment in the study population, (4) matched control subjects, (5) an adequate description of the process of control selection, and (6) inclusion of sufficient data to calculate ORs and 95% CIs

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Sudden infant death syndrome	Any breast feeding vs no breast feeding	Statistically significant: 726/1410 vs 3179/4139 aOR: 0.55, 95%CI [0.44;0.69] (p<0.00001) *In favour of breast feeding*	7, 1410 vs 4139	Hauck, 2011

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	0	See systematic review Hauck 2011
Imprecision	0	
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is limited evidence in favour of breast feeding. It was shown that any breast feeding resulted in a statistically significant decreased risk of sudden infant death, compared to no breast feeding (Hauck 2011). Evidence is of low quality.
Reference(s)	**Systematic reviews** Hauck FR, Thompson JM, Tanabe KO, Moon RY, Vennemann MM. *Breastfeeding and reduced risk of sudden infant death syndrome: a meta-analysis*. Pediatrics. 2011, 128(1):103-110.

Sudden infant death syndrome (SIDS) – Home monitoring device (Prevention)

Question (PICO)	In babies (P), is using a home monitoring device (I) compared to not using a home monitoring device (C) effective to prevent sudden infant death syndrome (O)?
Search Strategy	Databases **The Cochrane Library** for systematic reviews using the following search strategy: 1. [mh sudden infant death] OR "sudden infant death":ti,ab,kw OR "SID":ti,ab,kw OR "SIDS":ti,ab,kw OR "Crib death":ti,ab,kw OR "Cot death":ti,ab,kw 2. [mh meta-analysis] OR meta analys*:ti,ab,kw OR meta-analys*:ti,ab,kw OR 'cochrane':ti,ab,kw OR 'embase':ti,ab,kw OR 'pubmed':ti,ab,kw OR 'medline':ti,ab,kw OR 'reference list':ti,ab,kw OR 'reference lists':ti,ab,kw OR 'bibliography':ti,ab,kw OR 'bibliographies':ti,ab,kw OR 'hand-search':ti,ab,kw OR 'manual search':ti,ab,kw OR 'selection criteria':ti,ab,kw OR 'relevant journals':ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for systematic reviews using the following search strategy: 1. "Sudden infant death"[Mesh] OR "sudden infant death"[TIAB] OR "SID"[TIAB] OR "SIDS"[TIAB] OR "Crib death"[TIAB] OR "Cot death"[TIAB] 2. "Guideline "[Publication Type] OR "Practice Guidelines as Topic"[Mesh] OR "Practice Guideline "[Publication Type] OR practice guideline*[TIAB] OR Meta-Analysis as Topic[Mesh] OR meta analy*[TIAB] OR metaanaly*[TIAB] OR Meta-Analysis[Publication Type] OR systematic review*[TIAB] OR systematic overview*[TIAB] OR Review Literature as Topic[Mesh] OR cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB] OR reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB] OR selection criteria[TIAB] OR data extraction[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) for systematic reviews using the following search strategy: 1. 'Sudden infant death'/exp OR 'sudden infant death':ab,ti OR 'SID':ab,ti OR 'SIDS':ab,ti OR "Crib death":ab,ti OR "Cot death":ab,ti 2. 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti 3. 1-2 AND **The Cochrane Library** for controlled trials using the following search strategy: 1. [mh sudden infant death] OR "sudden infant death":ti,ab,kw OR "SID":ti,ab,kw OR "SIDS":ti,ab,kw OR "Crib death":ti,ab,kw OR "Cot death":ti,ab,kw 2. [mh home nursing] OR "home nursing":ti,ab,kw OR "home care":ti,ab,kw OR "home monitoring":ti,ab,kw 3. 1-2 AND Filter: 2013-2015 **MEDLINE** (via PubMed interface) for individual studies using the following search strategy: 1. "Sudden infant death"[Mesh] OR "sudden infant death"[TIAB] OR "SID"[TIAB] OR "SIDS"[TIAB] OR "Crib death"[TIAB] OR "Cot death"[TIAB]

	2. "home nursing"[Mesh] OR "home nursing"[TIAB] OR "home care"[TIAB] OR "home monitoring"[TIAB] 3. 1-2 AND Filter: 2013-2015 **Embase** (via Embase.com interface) for individual studies using the following search strategy: 1. 'Sudden infant death'/exp OR 'sudden infant death':ab,ti OR 'SID':ab,ti OR 'SIDS':ab,ti OR "Crib death":ab,ti OR "Cot death":ab,ti 2. 'home care'/exp OR 'home nursing':ab,ti OR 'home care':ab,ti OR 'home monitoring':ab,ti 3. 1-2 AND Filter: 2013-2015 Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	14 July 2015
In/Exclusion criteria	**Population:** Included: infants under age of 2 **Intervention:** Include: Home monitoring (including apnoea monitoring, respiratory monitoring and cardiorespiratory monitoring). **Comparison:** Include: home monitoring with some form of normal practice **Outcome:** Include: sudden infant death. Exclude: other direct health-related outcomes than sudden infant death **Study design:** Include: a systematic review was included if the search strategy and selection criteria are clearly described and if at least MEDLINE and one other relevant database was searched. If no systematic review was published within the last 5 years, individual experimental and/or observational studies were included. Exclude: case series, animal studies, *ex vivo* or *in vitro* studies. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline)

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Ariagno, 1983, USA	Observational: cohort study	156 infants with previous apparent life-threatening events, 104 term, 33 pre-term	Intervention: Cardiorespiratory monitors triggered by apnea or bradycardia Control: no monitoring	Cited in systematic review Strehle 2012
Strehle, 2012, United Kingdom	Systematic review	Eleven experimental/observational studies involving infants under 2 years of age	Intervention: home monitoring (including apnea monitoring, respiratory monitoring and cardiorespiratory monitoring). Control: home monitoring with some form of normal practice	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Sudden infant death syndrome	Monitoring vs no monitoring	Not statistically significant: 0/137 vs 1/19 § RR: 0.05, 95%CI [0.00;1.15] ¥ (p=0.06) *	1, 137 vs 19	Ariagno, 1983

¥ Imprecision (large variability of results)

§ Imprecision (limited sample size or low number of events)

* Calculations done by the reviewer(s) using Review Manager software

Quality of evidence

Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations
Ariagno, 1983	No	No	No	No	No

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Low number of events and large variability in results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Conclusion	There is limited evidence neither in favour of monitoring devices nor not using monitoring devices. A statistically significant decreased risk of sudden infant death syndrome, using monitoring devices compared to not using these could not be demonstrated (Ariagno 1983). Evidence is of very low quality and results of this study are imprecise due to limited sample size and large variability of results.
Reference(s)	**Articles** Ariagno RL, Guilleminault C, Korobkin R, Owen-Boeddiker M, Baldwin R. *'Near-miss' for sudden infant death syndrome infants: a clinical problem*. Pediatrics. 1983 May;71(5):726-30. **Systematic reviews** Strehle EM, Gray WK, Gopisetti S, Richardson J, McGuire J, Malone S. Can home monitoring reduce mortality in infants at increased risk of sudden infant death syndrome? A systematic review. Acta Paediatr 2012, 101(1):8-13.

Sudden infant death syndrome (SIDS) – Bed sharing (Risk Factor)

Question (PICO)	In babies (P), is bed sharing (I) a risk factor for sudden infant death (O) compared to not bed sharing (C)?
Search Strategy	Databases **The Cochrane Library** for systematic reviews using the following search strategy: 1. [mh sudden infant death] OR "sudden infant death":ti,ab,kw OR "SID":ti,ab,kw OR "SIDS":ti,ab,kw OR "Crib death":ti,ab,kw OR "Cot death":ti,ab,kw 2. [mh meta-analysis] OR meta analys*:ti,ab,kw OR meta-analys*:ti,ab,kw OR 'cochrane':ti,ab,kw OR 'embase':ti,ab,kw OR 'pubmed':ti,ab,kw OR 'medline':ti,ab,kw OR 'reference list':ti,ab,kw OR 'reference lists':ti,ab,kw OR 'bibliography':ti,ab,kw OR 'bibliographies':ti,ab,kw OR 'hand-search':ti,ab,kw OR 'manual search':ti,ab,kw OR 'selection criteria':ti,ab,kw OR 'relevant journals':ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for systematic reviews using the following search strategy: 1. "Sudden infant death"[Mesh] OR "sudden infant death"[TIAB] OR "SID"[TIAB] OR "SIDS"[TIAB] OR "Crib death"[TIAB] OR "Cot death"[TIAB]

	2. "Guideline "[Publication Type] OR "Practice Guidelines as Topic"[Mesh] OR "Practice Guideline "[Publication Type] OR practice guideline*[TIAB] OR Meta-Analysis as Topic[Mesh] OR meta analy*[TIAB] OR metaanaly*[TIAB] OR Meta-Analysis[Publication Type] OR systematic review*[TIAB] OR systematic overview*[TIAB] OR Review Literature as Topic[Mesh] OR cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB] OR reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB] OR selection criteria[TIAB] OR data extraction[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) for systematic reviews using the following search strategy: 1. 'Sudden infant death'/exp OR 'sudden infant death':ab,ti OR 'SID':ab,ti OR 'SIDS':ab,ti OR "Crib death":ab,ti OR "Cot death":ab,ti 2. 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	14 July 2015
In/Exclusion criteria	**Population:** Included: infants **Intervention:** Include: bed sharing **Comparison:** Include: no bed sharing **Outcome:** Include: sudden infant death **Study design:** Include: a systematic review was included if the search strategy and selection criteria are clearly described and if at least MEDLINE and one other relevant database was searched. If no systematic review was published within the last 5 years, individual experimental and/or observational studies were included. Exclude: case series**,** animal studies, *ex vivo* or *in vitro* studies. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline)

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Das, 2014, India	Systematic review	21 observational studies that included infants in the first 4 weeks of life who died (sudden infant death syndrome, cases) or not (controls)	Risk factor: bed sharing Control: no bed sharing	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Sudden infant death syndrome	Routine bed sharing vs no bed sharing	Statistically significant: 178/997 vs 271/2699 (multivariate) OR: 2.22, 95%CI [1.71;2.87] ($p<0.05$) *In favour of no bed sharing*	6, 997 vs 2699	Das, 2014

	Last night bed sharing vs no bed sharing	Statistically significant: 320/1527 vs 614/6708 (multivariate) OR: 2.51, 95%CI [1.95;3.23] (p<0.05) *In favour of no bed sharing*	7, 1527 vs 6708	

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	-1	See systematic review Das 2014
Imprecision	0	
Inconsistency	0	
Indirectness	-1	
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Conclusion	There is limited evidence with harm for bed sharing. It was shown that bed sharing (routine/last night) resulted in a statistically significant increased risk of sudden infant death, compared to no bed sharing (Das 2014). Evidence is of very low quality.
Reference(s)	**Systematic reviews** Das RR, Sankar MJ, Agarwal R, Paul VK. Is "Bed Sharing" Beneficial and Safe during Infancy? A Systematic Review. Int J Pediatr. 2014, 2014:468538.

Sudden infant death syndrome (SIDS) – Room temperature (Risk Factor)

Question (PICO)	In babies (P) is a higher room temperature (RF) compared to a lower room temperature (C) a risk factor for sudden infant death syndrome (O)?
Search Strategy	Databases **The Cochrane Library** for systematic reviews using the following search strategy: 1. [mh sudden infant death] OR "sudden infant death":ti,ab,kw OR "SID":ti,ab,kw OR "SIDS":ti,ab,kw OR "Crib death":ti,ab,kw OR "Cot death":ti,ab,kw 2. [mh meta-analysis] OR meta analys*:ti,ab,kw OR meta-analys*:ti,ab,kw OR 'cochrane':ti,ab,kw OR 'embase':ti,ab,kw OR 'pubmed':ti,ab,kw OR 'medline':ti,ab,kw OR 'reference list':ti,ab,kw OR 'reference lists':ti,ab,kw OR 'bibliography':ti,ab,kw OR 'bibliographies':ti,ab,kw OR 'hand-search':ti,ab,kw OR 'manual search':ti,ab,kw OR 'selection criteria':ti,ab,kw OR 'relevant journals':ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for systematic reviews using the following search strategy: 1. "Sudden infant death"[Mesh] OR "sudden infant death"[TIAB] OR "SID"[TIAB] OR "SIDS"[TIAB] OR "Crib death"[TIAB] OR "Cot death"[TIAB] 2. "Guideline "[Publication Type] OR "Practice Guidelines as Topic"[Mesh] OR "Practice Guideline "[Publication Type] OR practice guideline*[TIAB] OR Meta-Analysis as Topic[Mesh] OR meta analy*[TIAB] OR metaanaly*[TIAB] OR Meta-Analysis[Publication Type] OR systematic review*[TIAB] OR systematic overview*[TIAB] OR Review Literature as Topic[Mesh] OR cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB] OR reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB] OR selection criteria[TIAB] OR data extraction[TIAB] 3. 1-2 AND

	Embase (via Embase.com interface) for systematic reviews using the following search strategy: 1. 'Sudden infant death'/exp OR 'sudden infant death':ab,ti OR 'SID':ab,ti OR 'SIDS':ab,ti OR "Crib death":ab,ti OR "Cot death":ab,ti 2. 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti 3. 1-2 AND **The Cochrane Library** for clinical trials using the following search strategy: 1. [mh sudden infant death] OR "sudden infant death":ti,ab,kw OR "SID":ti,ab,kw OR "SIDS":ti,ab,kw OR "Crib death":ti,ab,kw OR "Cot death":ti,ab,kw 2. "room temperature":ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for individual studies using the following search strategy: 1. "Sudden infant death"[Mesh] OR "sudden infant death"[TIAB] OR "SID"[TIAB] OR "SIDS"[TIAB] OR "Crib death"[TIAB] OR "Cot death"[TIAB] 2. "room temperature"[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) for individual studies using the following search strategy: 1. 'Sudden infant death'/exp OR 'sudden infant death':ab,ti OR 'SID':ab,ti OR 'SIDS':ab,ti OR "Crib death":ab,ti OR "Cot death":ab,ti 2. 'room temperature':ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	14 July 2015
In/Exclusion criteria	**Population:** Included: infants **Intervention:** Include: higher room temperature **Comparison:** Include: lower room temperature **Outcome:** Include: sudden infant death **Study design:** Include: a systematic review was included if the search strategy and selection criteria are clearly described and if at least MEDLINE and one other relevant database was searched. If no systematic review was published within the last 5 years, individual experimental and/or observational studies were included. Exclude: case series**,** animal studies, *ex vivo* or *in vitro* studies. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline)

Characteristics of included studies

Author, year, Country	Study design	Population	Risk factor	Remarks
Ponsonby, 1992, Australia	Observational: case-control study	Infants who died (cases) were matched with two controls (controls), one for age and one for age and birth weight.	Higher room temperature vs lower room temperature	Thermal measurements were conducted at the death scene for cases and at the scene of last sleep for control infants, who were visited unexpectedly within four weeks of the index

				infant's death on a day of similar climatic conditions.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Sudden infant death syndrome	Higher versus lower room temperature (reflected by the thermal insulation unit (tog= 10 times the temperature difference in °C between its two faces when the heat flow is equal to 1 w/m^2)	Statistically significant: no information on (absolute)numbers available aRR: 1.26, 95%CI [1.05;1.52] (p<0.05) *In favour of lower room temperature*	1, 28 vs 40 §	Ponsonby, 1992

§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations
Ponsonby, 1992	No	No	No	No	No

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Limited sample size
Inconsistency	0	
Indirectness	-1	Risk factor: tog unit instead of °C
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [C]**	

Conclusion	There is limited evidence with harm for a higher room temperature (i.e. excess thermal insulation) . It was shown that higher thermal insulation for their given room temperature resulted in a statistically significant increased risk of sudden infant death, compared to lower thermal insulation (Ponsonby, 1992). Evidence is of very low quality.
Reference(s)	**Articles** Ponsonby AL, Dwyer T, Gibbons LE, Cochrane JA, Jones ME, McCall MJ. *Thermal environment and sudden infant death syndrome: case-control study*. BMJ 1992, 304(6822):277-82.

Sudden infant death syndrome (SIDS) – Pacifier (Risk Factor)

Question (PICO)	In babies (P), is using a pacifier (I) a risk factor for sudden infant death (O) compared to not using a pacifier (C)?
Search Strategy	Databases **The Cochrane Library** for systematic reviews using the following search strategy: 1. [mh sudden infant death] OR "sudden infant death":ti,ab,kw OR "SID":ti,ab,kw OR "SIDS":ti,ab,kw OR "Crib death":ti,ab,kw OR "Cot death":ti,ab,kw 2. [mh meta-analysis] OR meta analys*:ti,ab,kw OR meta-analys*:ti,ab,kw OR 'cochrane':ti,ab,kw OR 'embase':ti,ab,kw OR 'pubmed':ti,ab,kw OR 'medline':ti,ab,kw OR 'reference list':ti,ab,kw OR 'reference lists':ti,ab,kw OR 'bibliography':ti,ab,kw OR 'bibliographies':ti,ab,kw OR 'hand-search':ti,ab,kw OR 'manual search':ti,ab,kw OR 'selection criteria':ti,ab,kw OR 'relevant journals':ti,ab,kw

	3. 1-2 AND **MEDLINE** (via PubMed interface) for systematic reviews using the following search strategy: 1. "Sudden infant death"[Mesh] OR "sudden infant death"[TIAB] OR "SID"[TIAB] OR "SIDS"[TIAB] OR "Crib death"[TIAB] OR "Cot death"[TIAB] 2. "Guideline "[Publication Type] OR "Practice Guidelines as Topic"[Mesh] OR "Practice Guideline "[Publication Type] OR practice guideline*[TIAB] OR Meta-Analysis as Topic[Mesh] OR meta analy*[TIAB] OR metaanaly*[TIAB] OR Meta-Analysis[Publication Type] OR systematic review*[TIAB] OR systematic overview*[TIAB] OR Review Literature as Topic[Mesh] OR cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB] OR reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB] OR selection criteria[TIAB] OR data extraction[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) for systematic reviews using the following search strategy: 1. 'Sudden infant death'/exp OR 'sudden infant death':ab,ti OR 'SID':ab,ti OR 'SIDS':ab,ti OR "Crib death":ab,ti OR "Cot death":ab,ti 2. 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti 3. 1-2 AND **The Cochrane Library** for clinical trials using the following search strategy: 1. [mh sudden infant death] OR "sudden infant death":ti,ab,kw OR "SID":ti,ab,kw OR "SIDS":ti,ab,kw OR "Crib death":ti,ab,kw OR "Cot death":ti,ab,kw 2. [mh pacifiers] OR "pacifier":ti,ab,kw 3. 1-2 AND Filter: 2006-2015 **MEDLINE** (via PubMed interface) for individual studies using the following search strategy: 1. "Sudden infant death"[Mesh] OR "sudden infant death"[TIAB] OR "SID"[TIAB] OR "SIDS"[TIAB] OR "Crib death"[TIAB] OR "Cot death"[TIAB] 2. "pacifiers"[Mesh] OR "pacifier"[TIAB] 3. 1-2 AND Filter: 2006-2015 **Embase** (via Embase.com interface) for individual studies using the following search strategy: 1. 'Sudden infant death'/exp OR 'sudden infant death':ab,ti OR 'SID':ab,ti OR 'SIDS':ab,ti OR "Crib death":ab,ti OR "Cot death":ab,ti 2. 'pacifier'/exp OR 'pacifier':ab,ti 3. 1-2 AND Filter: 2006-2015 Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	14 July 2015
In/Exclusion criteria	**Population:** Included: infants **Intervention:** Include: pacifier use

	Comparison: Include: no pacifier use **Outcome:** Include: sudden infant death. Exclude: other direct health-related outcomes than sudden infant death **Study design:** Include: a systematic review (of diagnostic accuracy studies) was included if the search strategy and selection criteria are clearly described and if at least MEDLINE and one other relevant database was searched. If no systematic review was published within the last 5 years, individual experimental and/or observational studies were included. Exclude: case series**,** animal studies, *ex vivo* or *in vitro* studies. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline)

Characteristics of included studies

Author, year, Country	Study design	Population	Risk factor	Remarks
Hauck, 2005, USA	Systematic review	Meta-analyses of 9 observational (case-control) studies (1987-1996) that include data about the association between pacifiers and sudden infant death syndrome, involving 2060 infants with sudden infant death syndrome (cases) and 6676 infants without sudden infant death syndrome (controls).	Pacifier use vs no pacifier use	Included studies were performed in Western countries (Europe, USA, United Kingdom, Norway, Ireland, New Zealand, Scotland and The Netherlands)

Synthesis of findings

Outcome	Risk factor	Effect Size	#studies, # participants	Reference
Sudden infant death syndrome	Usual pacifier use vs no pacifier use	Statistically significant: 796/1568 vs 3147/5886 (multivariate) OR: 0.71, 95%CI [0.59;0.85] (p<0.001) *In favour of usual pacifier use*	4, 1568 vs 5886	Hauck, 2005
	"Last sleep" pacifier use (i.e. the period of sleep during which the infant died) vs no pacifier use	Statistically significant: 412/1779 vs 2122/5638 (multivariate) OR: 0.39, 95%CI [0.31;0.50] (p<0.001) *In favour of "last sleep" pacifier use*	7, 1779 vs 5638	

Quality of evidence

Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations
Hauck, 2005	No	No	No	No	No

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	0	
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is limited evidence with benefit for pacifier use.

	It was shown that usual/"last sleep" pacifier use resulted in a statistically significant decreased risk of sudden infant death syndrome, compared to no pacifier use (Hauck 2005). Evidence is of low quality.
Reference(s)	**Articles** Hauck FR, Omojokun OO, Siadaty MS. *Do pacifiers reduce the risk of sudden infant death syndrome? A meta-analysis*. Pediatrics. 2005 Nov;116(5):e716-23.

Sudden infant death syndrome (SIDS) – Sleeping in parent's room (Risk Factor)

Question (PICO)	In infants of up to 6 months (P), is not sharing a room with the parents (RF), compared to sharing a room with the parents (C), a risk factor for sudden infant death syndrome (SIDS) (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "sudden infant death"] OR "sudden infant death":ti,ab,kw OR "sudden infant death syndrome":ti,ab,kw OR "SID":ti,ab,kw OR "SIDS":ti,ab,kw OR (crib NEXT death*):ti,ab,kw OR (cot NEXT death*):ti,ab,kw OR (unexpected infant NEXT death*):ti,ab,kw 2. "room sharing":ti,ab,kw OR "roomsharing":ti,ab,kw OR co-sleeping:ti,ab,kw OR "co sleeping":ti,ab,kw OR (sleep AND parents):ti,ab,kw OR (room AND shar*):ti,ab,kw 3. #1 AND #2 **MEDLINE** (via PubMed interface) for systematic reviews, experimental and observational studies using the following search strategy: 1. "Sudden infant death"[MeSH] OR "sudden infant death"[TIAB] OR "sudden infant death syndrome"[TIAB] OR SID[TIAB] OR SIDS[TIAB] OR crib death*[TIAB] OR cot death*[TIAB] OR unexpected infant death*[TIAB] 2. "room sharing"[TIAB] OR "roomsharing"[TIAB] OR "cosleeping"[TIAB] OR "co sleeping"[TIAB] OR (sleep[TIAB] AND parents[TIAB]) OR (room[TIAB] AND shar*[TIAB]) 3. 1-2 AND **Embase** (via Embase.com interface) for systematic reviews, experimental and observational studies using the following search strategy: 1. 'sudden infant death syndrome'/exp OR 'sudden infant death':ab,ti OR 'sudden infant death syndrome':ab,ti OR (crib NEXT/1 death*):ab,ti OR (cot NEXT/1 death*):ab,ti OR (unexpected infant NEXT/1 death*):ab,ti 2. 'vaccination'/exp OR 'vaccine'/exp OR vaccin*:ab,ti OR (active NEXT/1 immunization*):ab,ti OR (active NEXT/1 immunisation*):ab,ti OR immunization*:ab,ti OR immunisation*:ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	21 January 2016
In/Exclusion criteria	**Population:** Include: Infants of < 2 years old. Exclude: Infants of > 2 years old. **Risk factor:** Include: Not sharing a room with parents. Exclude: Sharing a bed with parents or any other intervention to prevent SIDS. **Comparison:** Include: Sharing a room with the parents. **Outcome:** Include: SIDS.

	Study design: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Only studies which performed multivariate analyses were included. Exclude: observational studies if intervention is already included in experimental studies, case series, cross-sectional studies, animal studies, ex vivo or in vitro studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values, studies only performing univariate analyses. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Risk factor	Remarks
Blair, 1999, UK	Observational: Case-control study	Infants, 321 cases and 1299 controls, aged 7-364 days old.	Sleeping location for last sleep: solitary sleeper vs room sharer vs bed sharer (and put back in own cot) vs bed sharer (at end of sleep) vs sofa sharer Routine sleeping location: Solitary vs room Sharer vs bed sharer [only data for room sharer vs solitary sleeper was extracted]	Questionnaire of in total 600 fields, including demographic and social data; the medical history of the infant and other family members; use of cigarettes, alcohol, and drugs; the precise sleeping arrangements for the infant; and full details of the events preceding and the circumstances surrounding the death was used. Data was used to control for significant outcomes in multivariate analysis
Blair, 2009, UK	Observational: Case-control study	Infants, 79 cases, 87 random controls and 82 high-risk of SIDS controls, all below 2 years of age [Data from high-risk of SIDS controls was not extracted]	Sleeping location for last sleep: Sleeping in room without parent vs sleeping in room with parent vs sleeping in bed vs sofa with parent [only data for room sharer vs solitary sleeper was extracted]	Parents were interviewed via a detailed questionnaire. Significant parameters, in addition to age and daytime/night-time sleep, were added to control for in a multivariate analysis.
Carpenter, 2004, UK	Observational: Case-control study	Infants, 745 cases and 2411 controls.	Sleeping location for last sleep: Room shared (but not bed) vs room not shared Routine sleeping location:	Data was collected in centres all over Europe. Parents were interviewed via a questionnaire, in total 56 variables were collected, of which 32 were approximately

			Room shared (but not bed) vs room not shared	complete over the different centres.
Carpenter, 2013, UK	Observational: Case-control study	Infants, 1472 cases and 4679 controls, aged < 1 year.	Sleeping location for last sleep: Room shared vs room not shared	Raw data was collected and pooled from 5 different studies (Carpenter, 2004; McGarvey, 2006; Mitchell, 1992;Tappin, 2005;Vennemann, 2009) after contacting the authors. These studies did not all report the outcome room sharing, because of which individual studies that did report this outcome were also included in this summary.
Scragg, 1996, New Zealand	Observational: Case-control study	Infants, 393 cases and 1592 controls, aged 28-365 days	Sleeping location during last 2 weeks: Shared with adult vs shared with child vs slept alone Sleeping location during last night: Shared with adult vs shared with child vs slept alone [Only data for room sharing with adult vs sleeping alone was extracted]	Data was collected through interviews of approx. 75 min
Tappin, 2005, UK	Observational: Case-control study	Infants, 123 cases and 263 controls.	Sleeping location during last sleep: Room sharing with parents vs Bed sharing with parents vs Separate room vs Separate room with some bed sharing vs Couch sharing vs Chair sharing vs Cot sharing with twin [Only data from room sharing vs separate room was extracted]	Data was collected through a questionnaire for core medical and social data, and infant-care practices used routinely and for the night before interview for controls and day/night of death for SIDS.
Vennemann, 2009, Germany	Observational: Case-control study	Infants, 333 cases and 998 controls.	Sleeping location during last 4 weeks: Own room or with siblings vs parent's room vs living room vs outside vs everything else Sleeping location during last sleep:	Parents were interviewed via a detailed questionnaire

			Own room or with siblings vs parent's room vs living room vs at friends' vs outside vs everything else [Only data from own room or with siblings vs parent's room were extracted]	

Synthesis of findings

Outcome	Risk factor	Effect Size	#studies, # participants	Reference
SIDS	Solitary sleeping vs room sharing as usual sleep location	Not statistically significant: 77/266 vs 410/1223 OR: 0.88, 95%CI [0.62-1.25] ¥ (p>0.05)	1, 266 vs 1223	Blair, 1999
	Solitary sleeping vs room sharing as last sleep location	Statistically significant: 114/195 vs 420/926 aOR: 10.49, 95%CI [4.26-25.81] (p<0.05) *With harm for solitary sleeping*	1, 195 vs 926	
		Statistically significant: 21/36 vs 21/69 aOR: 21.34, 95%CI [2.99-152.56] (p=0.002) *With harm for solitary sleeping*	1, 36 vs 69 §	Blair, 2009
	Room shared vs room not shared as usual sleep location	Statistically significant: 180/385 vs 816/1388 aOR: 0.48, 95%CI [0.34-0.69] (p<0.05) *With harm for room not shared*	1, 385 vs 1388	Carpenter, 2004
	Room shared vs room not shared as last sleep location	Statistically significant: 93/332 vs 474/1065 aOR: 0.32, 95%CI [0.19-0.55] *With harm for room not shared*	1, 332 vs 1065	
		Statistically significant: 617/1434 vs 1823/4629 aOR: 2.4, 95%CI [2.0-2.9] p<0.05) *With harm for room not shared*	5, 1434 vs 4629	Carpenter, 2013
	Room shared with adult during last 2 weeks vs sleeping alone during last 2 weeks	Statistically significant: 238/391 vs 970/1590 aOR: 0.29, 95%CI [0.2-0.42] (p<0.05) *With harm for sleeping alone during last 2 weeks*	1, 393 vs 1592	Scragg, 1996
	Room shared with adult during last night vs sleeping alone during last night	Statistically significant: 165/387 vs 747/1556 aOR: 0.26, 95%CI [0.18-0.37] (p<0.05) *With harm for sleeping alone during last night*	1, 387 vs 1556	
	Separate room vs room shared with parent during last night	Statistically significant: 15/59 vs 43/210 aOR: 3.26, 95%CI [1.03-10.35]	1, 123 vs 263 §	Tappin, 2005

		(p<0.05) *With harm for separate room*		
	Own room or with siblings vs parent's room during last night	Not statistically significant: 129/265 vs 386/831 aOR: 1.72, 95%CI [0.97-3.04] ¥ (p>0.05)	1, 333 vs 998	Vennemann, 2009
	Own room or with siblings vs parent's room during last 4 weeks	Not statistically significant: 119/278 vs 373/807 aOR: 1.47, 95%CI [0.85-2.52] ¥ (p>0.05)		

¥ Imprecision (large variability of results)

§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations
Blair, 1999	No	Yes, questionnaires/interviews may lead to recall bias. However in the case of recalling where baby slept this might be of lesser importance	No, controlled for maternal age, parity, gestational age, birth weight, multiple births, unemployment, overcrowding, maternal smoking during pregnancy, paternal smoking, paternal drug use, daily postnatal exposure to tobacco smoke, previous episode of apparent life threatening event according to parents, maternal anxiety over infant becoming too hot, infant put down in prone or side position for last sleep, infant being found after last sleep with bedcovers over head, use of dummy for any part of last sleep, use of pillow, recent maternal alcohol consumption before last sleep, parental estimate of poor health, parental tiredness, change in routine affecting infant, sleeping under duvet and thickness.	No	No
Blair, 2009	No	Yes, questionnaires/interviews may lead to recall bias. However in the case of recalling where baby	No, controlled for infant's age, daytime or night time sleep, maternal alcohol consumption, bed sharing, maternal smoking during pregnancy, infant	No	No

		slept this might be of lesser importance	swaddling, maternal educational qualifications, prone sleeping, gestational age, parity, sleeping on pillow, infant's health during last 24h.		
Carpenter, 2004	No	Yes, questionnaires/interviews may lead to recall bias. However in the case of recalling where baby slept this might be of lesser importance	No, controlled for sleeping position, maternal smoking, bed sharing, others in the household smoking, dummy use, history of apparent life threatening event, sex, multiple birth, birth weight, admitted to special care baby unit, urinary tract infection during pregnancy, maternal age, parity, marital status, parental unemployment, head covered, sweating, duvet used during last sleep, dummy used during last sleep, interval since last birth, maternal alcohol consumption prior to last sleep, maternal drug use since birth, moved house since birth	No, data was collected over 20 different centres, and missing data was estimated and added, based on closely related variables.	No
Carpenter, 2013	No	Yes, questionnaires/interviews may lead to recall bias. However in the case of recalling where baby slept this might be of lesser importance	No, controlled for bed sharing, breast feeding, sleeping position, parental smoking, maternal alcohol consumption during last 24h, maternal drug use after birth, gender, race, birth weight, age, parity, marital status.	No, data from 5 different studies was pooled, and missing data estimated and added, based on a software model.	No
Scragg, 1996	No	Yes, questionnaires/interviews may lead to recall bias. However in the case of recalling where baby slept this might be of lesser importance	No, controlled for maternal age, maternal education, maternal age at first pregnancy, parity, attendance of antenatal clinics and classes, sex, gestational age, birth weight, neonatal unit acceptance, marital status, maternal employment, region of residence, dummy use, breastfeeding, sleeping position, age of infant, season, time of day at	No	No

			death, bed sharing, maternal smoking.		
Tappin, 2005	No	Yes, questionnaires/interviews may lead to recall bias. However in the case of recalling where baby slept this might be of lesser importance	No, controlled for maternal age, quadratic function of maternal age, birth weight, infant age, parity, either parent smoked, laid prone to sleep, laid on side to sleep, found with head covered in the past, found with head covered after last sleep, infant routinely slept on a used infant mattress.	No	No
Venneman n, 2009	No	Yes, questionnaires/interviews may lead to recall bias. However in the case of recalling where baby slept this might be of lesser importance	No, controlled for the analysis of the reference sleep, maternal smoking in pregnancy, maternal family status, maternal age at delivery, socioeconomic status of the family (socioeconomic status [SES] was calculated by using school education, present work position, and income), previous live births, birth weight of the infant, not breastfeeding for at least the first 2 weeks of life, bed sharing in the last night, pillow in the infants bed, additional heating during the last sleep (a hot water bottle in the infants bed or the bed in front of a heater), position place to sleep, pacifier use during the last sleep	No	No

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	0	
Imprecision	0	
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion(s)	There is limited evidence with benefit for an infant sleeping in the parent's bedroom regarding the prevalence of sudden infant death syndrome: It was shown that sleeping an infant in the parent's bedroom resulted in a statistically significant decreased risk of sudden infant death syndrome, compared to sleeping in a

	room alone during its last sleep (Blair 1999; Blair 2009; Carpenter 2004, Carpenter 2013; Scragg 1996;Tappin 2005). Furthermore, It was shown that the habit of an infant to sleep in the parent's bedroom resulted in a statistically significant decreased risk of sudden infant death syndrome, compared to the habit of sleeping in a room alone (Carpenter 2004, Scragg 1996). Evidence is of low quality. In contrast, there is limited evidence neither for the benefit of an infant sleeping in the parent's room nor sleeping in a room alone: A statistically significant decreased risk of sudden infant death syndrome in case of the infant having the habit of sleeping in the parent's bedroom compared to sleeping in a room alone could not be demonstrated (Blair 1999, Vennemann 2009) Evidence is of low quality and results of these studies are imprecise due to a large variability of results.
Reference(s)	**Articles** Blair PS, Fleming PJ, Smith IJ, Platt MW, Young J, Nadin P, Berry PJ, Golding J. *Babies sleeping with parents: case-control study of factors influencing the risk of the sudden infant death syndrome. CESDI SUDI research group.* BMJ. 1999 Dec 4;319(7223):1457-61. Blair PS, Sidebotham P, Evason-Coombe C, Edmonds M, Heckstall-Smith EM, Fleming P. *Hazardous cosleeping environments and risk factors amenable to change: case-control study of SIDS in south west England.* BMJ. 2009 Oct 13;339:b3666. Carpenter RG, Irgens LM, Blair PS, England PD, Fleming P, Huber J, Jorch G, Schreuder P. *Sudden unexplained infant death in 20 regions in Europe: case control study.* Lancet. 2004 Jan 17;363(9404):185-91. Carpenter R, McGarvey C, Mitchell EA, Tappin DM, Vennemann MM, Smuk M, Carpenter JR. *Bed sharing when parents do not smoke: is there a risk of SIDS? An individual level analysis of five major case-control studies.* BMJ Open. 2013 May 28;3(5). pii: e002299. Scragg RK, Mitchell EA, Stewart AW, Ford RP, Taylor BJ, Hassall IB, Williams SM, Thompson JM. *Infant room-sharing and prone sleep position in sudden infant death syndrome. New Zealand Cot Death Study Group.* Lancet. 1996 Jan 6;347(8993):7-12. Tappin D, Ecob R, Brooke H. *Bedsharing, roomsharing, and sudden infant death syndrome in Scotland: a case-control study.* J Pediatr. 2005 Jul;147(1):32-7. Vennemann MM, Bajanowski T, Brinkmann B, Jorch G, Sauerland C, Mitchell EA; GeSID Study Group. *Sleep environment risk factors for sudden infant death syndrome: the German Sudden Infant Death Syndrome Study.* Pediatrics. 2009 Apr;123(4):1162-70.

Sudden infant death syndrome (SIDS) – Smoking (Risk Factor)

Question (PICO)	In babies (P), is smoking (RF) compared to no smoking of the parents (C) a risk factor for sudden infant death syndrome (SIDS) (O)?
Search Strategy	Databases **The Cochrane Library** using the following search strategy: 1. [mh "sudden infant death"] OR ("sudden infant death"):ti,ab,kw OR ("sudden infant death syndrome"):ti,ab,kw OR ("crib death*"):ti,ab,kw OR ("cot death*"):ti,ab,kw OR ("unexpected infant death*"):ti,ab,kw 2. [mh ethanol] OR [mh "alcohol drinking"] OR alcohol*:ti,ab,kw OR [mh "designer drugs"] OR [mh "street drugs"] OR drug*:ti,ab,kw OR [mh smoking] OR smok*:ti,ab,kw 3. [mh "risk"] OR (risk*):ti,ab,kw 4. 1 AND #2 AND #3 **MEDLINE** (via PubMed interface) using the following search strategy:

	1. "Sudden infant death"[MeSH] OR "sudden infant death"[TIAB] OR "sudden infant death syndrome"[TIAB] OR "SID*"[TIAB] OR "crib death*"[TIAB] OR "cot death*"[TIAB] OR "unexpected infant death*"[TIAB] 2. "Street drugs"[Mesh] OR "designer drugs"[Mesh] OR "ethanol"[Mesh] OR drug*[TIAB] OR alcohol*[TIAB] OR drunkenness[TIAB] OR "alcohol intoxication"[TIAB] OR "ethanol intoxication"[TIAB] OR "ethanol poisoning"[TIAB] OR "Smoking"[Mesh] OR smok*[TIAB] 3. "risk"[MeSH] OR "risk"*[TIAB] 4. 1-2-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'sudden infant death syndrome'/exp OR 'sudden infant death':ab,ti OR 'sudden infant death syndrome':ab,ti OR (crib NEXT/1 death*):ab,ti OR (cot NEXT/1 death*):ab,ti OR (unexpected infant NEXT/1 death*):ab,ti 2. 'street drug'/exp OR 'designer drug'/exp OR drug*:ab,ti OR 'alcohol'/exp OR alcohol*:ab,ti OR drunkenness*:ab,ti OR 'ethanol intoxication':ab,ti OR 'ethanol poisoning':ab,ti OR Smoking/exp OR smok*:ab,ti 3. 'risk'/exp OR risk*:ab,ti 4. 1-2-3 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	25 January 2016
In/Exclusion criteria	**Population:** Included: infants less than 1 year **Intervention:** Include: postnatal maternal smoking before SIDS **Comparison:** Include: postnatal maternal smoking before SIDS **Outcome:** Include: sudden infant death syndrome **Study design:** Include: a systematic review was included if the search strategy and selection criteria are clearly described and if at least MEDLINE and one other relevant database was searched. If no systematic review was published within the last 5 years, individual experimental and/or observational studies were included. Exclude: case reports, case series, animal studies, *ex vivo* or *in vitro* studies, letters, editorials, comments, opinion pieces, narrative reviews, modelling studies. **Language:** Include: English (only for newly identified evidence); English, French, German and Dutch. **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Zhang, 2013, China	Systematic review	Meta-analysis including 35 observational (case-control) studies, including 31,040 cases and 5,956,030 controls (23 studies available for prenatal maternal smoking analysis and 18 studies available for postnatal maternal smoking analysis, respectively). Trials were conducted in France, Sweden, England, New Zealand, Australia, America, Hungary, Germany, Netherlands, Norway, Scandinavian countries, Brazil, and Denmark between 1992 and 2011.	Risk factor: maternal smoking Control: no maternal smoking [only data of postnatal smoking were extracted]	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Sudden infant death syndrome	Postnatal maternal smoking vs no postnatal maternal smoking	Statistically significant: OR: 1.97, 95%CI [1.77; 2.19] ($p<0.05$) *With harm for postnatal maternal smoking.*	18, 2245 vs 4102	Zhang, 2013

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See systematic review; some infants death cases in which certain diagnosis are assumed without autopsy might actually be SIDS, could result in an overestimate of effects and could bias the results; plausibility of prenatal smoking effect, since mothers who smoked during pregnancy were very likely to smoke postnatally.
Imprecision	0	
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Moderate [B]**	

Conclusion	There is evidence with harm for postnatal maternal smoking. It was shown that postnatal smoking resulted in a statistically significant increased risk of sudden infant death syndrome (Zhang 2013). Evidence is of moderate quality.
Reference(s)	**Articles** Zhang K , Wang X. *Maternal smoking and increased risk of sudden infant death syndrome: A meta-analysis*. Legal medicine. 2013 15 (3):115-121.

Sudden infant death syndrome (SIDS) – Alcohol or drugs (Risk Factor)

Question (PICO)	In babies (P), is the use of alcohol or drugs by the parents (RF) compared to not using alcohol or drugs (C) a risk factor for sudden infant death syndrome (SIDS) (O)?
Search Strategy	Databases **The Cochrane Library** using the following search strategy: 1. [mh "sudden infant death"] OR ("sudden infant death"):ti,ab,kw OR ("sudden infant death syndrome"):ti,ab,kw OR ("crib death*"):ti,ab,kw OR ("cot death*"):ti,ab,kw OR ("unexpected infant death*"):ti,ab,kw 2. [mh ethanol] OR [mh "alcohol drinking"] OR alcohol*:ti,ab,kw OR [mh "designer drugs"] OR [mh "street drugs"] OR drug*:ti,ab,kw OR [mh smoking] OR smok*:ti,ab,kw 3. [mh "risk"] OR (risk*):ti,ab,kw 4. 1-3 AND **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Sudden infant death"[MeSH] OR "sudden infant death"[TIAB] OR "sudden infant death syndrome"[TIAB] OR "SID*"[TIAB] OR "crib death*"[TIAB] OR "cot death*"[TIAB] OR "unexpected infant death*"[TIAB] 2. "Street drugs"[Mesh] OR "designer drugs"[Mesh] OR "ethanol"[Mesh] OR drug*[TIAB] OR alcohol*[TIAB] OR drunkenness[TIAB] OR "alcohol

	intoxication"[TIAB] OR "ethanol intoxication"[TIAB] OR "ethanol poisoning"[TIAB] OR "Smoking"[Mesh] OR smok*[TIAB] 3. "risk"[MeSH] OR "risk*"[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'sudden infant death syndrome'/exp OR 'sudden infant death':ab,ti OR 'sudden infant death syndrome':ab,ti OR (crib NEXT/1 death*):ab,ti OR (cot NEXT/1 death*):ab,ti OR (unexpected infant NEXT/1 death*):ab,ti 2. 'street drug'/exp OR 'designer drug'/exp OR drug*:ab,ti OR 'alcohol'/exp OR alcohol*:ab,ti OR drunkenness*:ab,ti OR 'ethanol intoxication':ab,ti OR 'ethanol poisoning':ab,ti OR Smoking/exp OR smok*:ab,ti 3. 'risk'/exp OR risk*:ab,ti 4. 1-3 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	25 January 2016
In/Exclusion criteria	**Population:** Included: infants **Intervention:** Include: postnatal maternal use of alcohol or drugs before SIDS **Comparison:** Include: no postnatal maternal use of alcohol or drugs before SIDS **Outcome:** Include: sudden infant death syndrome (SIDS) **Study design:** Include: a systematic review was included if the search strategy and selection criteria are clearly described and if at least MEDLINE and one other relevant database was searched. If no systematic review was published within the last 5 years, individual experimental and/or observational studies were included. Exclude: case reports, case series, animal studies, *ex vivo* or *in vitro* studies, letters, editorials, comments, opinion pieces, narrative reviews, modelling studies. **Language:** Include: English (only for newly identified evidence); English, French, German and Dutch. **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Risk factor	Remarks
Alm, 1999, Sweden	Observational: Case-control	Infants, 7-364 old, 294 cases of SIDS and 869 controls	Risk factor: Alcohol consumption after pregnancy before SID Control: No alcohol consumption after pregnancy before SID	Nordic epidemiological SIDS study, parents invited by the local paediatrician (Norway and Sweden) or forensic institute (Denmark), data obtained through questionnaire between 1992-1995.
Blair, 1996, UK	Observational: Case-control	Infants aged 7-364 days old, 195 SID babies and 780 controls	Risk factor: Alcohol or drug use after pregnancy before SID Control: No alcohol or drug use after pregnancy before SID	Data collected at home by questionnaire between 1993-1997
Blair, 2009, UK	Observational: Case-control	Infants, from birth- 2 years old, 80 SIDS and 87 random controls and 82 high risk controls	Risk factor: Recent postnatal maternal alcohol consumption or drug use Control: no recent postnatal maternal alcohol consumption or drug use	Data collected at home by questionnaire between 2003-2006

		[data of high risk controls were not extracted]		
Carpenter, 2004, Uk	Observational: Case-control	Infants, 745 SID cases and 2411 controls	Risk factor: Recent postnatal maternal alcohol or drug use Control: no recent postnatal maternal alcohol drug use	Data were derived from case-control studies of SIDS of varying duration done in 20 centres between September, 1992, and April, 1996. Denmark, Norway, and Sweden, which comprised the Nordic study, were counted as three centres, as were the three regions (Yorkshire, Trent, and South West) that made up the first 2 years of the Confidential Enquiry into Stillbirths and Deaths in Infancy (CESDI) study in England.
Carpenter, 2013, UK	Observational: Case-control	Infants, less than 1 year old, 1472 SID cases and 4679 controls.	Risk factor: Recent postnatal maternal alcohol or drug use Control: no recent postnatal maternal alcohol drug use	Data obtained from 5 large databases were combined.
Klonoff-Cohen, 2001, USA	Observational: Case-control	Infants, between 1 week of age and 1 year of age, 239 SID cases and 239 controls	Risk factor: Postnatal maternal drug (Marijuana) use Control: No postnatal maternal alcohol drug (Marijuana) use	Data obtained by telephone interview (questionnaire) between 1989-1992
l'Hoir, 1998, The Netherlands	Observational: Case-control	Infants, between 7 days of age and 730 days of age, 73 SDIS and 146 controls	Risk factor: Postnatal maternal alcohol consumption Control: No postnatal maternal alcohol consumption	Data obtained at home by questionnaire between 1995 1996
Scragg, 1993, New Zealand	Observational: Case-control	Infants, between 28 days of age and 1 year of age, 393 SIDS and 1592 controls	Risk factor: Postnatal maternal alcohol consumption Control: Postnatal maternal alcohol consumption	Data obtained at home by interview between 1978-1990
Scragg, 2001, New Zealand	Observational: Case-control	Infants, 485 SIDS 1800 and controls	Risk factor: Postnatal maternal drug use Control: No postnatal maternal alcohol drug use	Data obtained at home by interview between 1978-1990

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Alcohol use				
Sudden infant death syndrome	Postnatal maternal alcohol consumption vs	Not statistically significant: Less than weekly: 111/235 vs 407/814;	1, 242 vs 859	Alm, 1999

	no postnatal maternal alcohol consumption	aOR: 0.9, 95%CI [0.6;1.3] ¥ (p=0.64) More than weekly: 7/131 vs 45/452 § aOR: 0.6, 95%CI [0.2;1.7] ¥ (p=0.31)		
	Alcohol in last 24h vs no alcohol in last 24h	Not statistically significant: ≥3 vs 0-2 units: 22/190 vs 35/778 § aOR: 1.91, 95%CI [0.97; 3.76] ¥ (p>0.05)	1, 190 vs 778	Blair, 1996
		Statistically significant: >2 units: 19/77 vs 2/87 § aOR: 41.62, 95%CI [5.45; 318.09] (p=0.0003) *With harm for alcohol use*	1, 77 vs 87	Blair, 2009
		Not statistically significant: 1-2 drinks: 50/518 vs 193/1847 § aOR: 1.00, 95%CI [0.63;1.57] ¥ (p>0.05) Statistically significant: 3 or more drinks: 39/507 vs 53/1707 § aOR: 2.33, 95%CI [1.28;4.21] (p<0.05) *With harm for alcohol consumption*	1, 557 vs 1900	Carpenter, 2004
		Statistically significant: 2 or more units 112/590 vs 99/1793 § aOR: 4.8, 95%CI [2.6;8.9] (p<0.05) *With harm for alcohol consumption*	5, 590 vs 1793	Carpenter, 2013
		Statistically significant: aOR: 2.25 95%CI[1.01;6.34] (p<0.05) £ *With harm for alcohol consumption*	1, 73 vs 146 §	l'Hoir, 1998
	Alcohol in the last month vs no alcohol in the last month	Statistically significant: 30/393 vs 381/1591 aOR: 0.55 95%CI[0.33;0.91] (p<0.05) *With harm for alcohol consumption*	1, 393 vs 1591	Scragg, 1993
Drug use				
Sudden infant death syndrome	Postnatal maternal drug use vs no postnatal maternal drug use	Statistically significant: 16/191 vs 11/777 § aOR: 2.80, 95%CI [1.10;7.18] (p<0.05) *With harm for drug use*	1, 191 vs 777	Blair, 1996
		Not statistically significant: 5/77 vs 2/87 § OR: 2.82, 95%CI [0.56; 14.14] ¥ (p=0.21)*	1, 77 vs 87	Blair, 2009
		Statistically significant: 21/568 vs 21/1909 §	1, 568 vs 1909	Carpenter, 2004

		aOR: 1.92, 95%CI [1.00;3.70] (p<0.05) *With harm for drug use*		
		Statistically significant: 21/603 vs 3/1828 § aOR: 11.5, 95%CI [2.2;59.5] (p<0.05) *With harm for drug use*	5, 603 vs 1828	Carpenter, 2013
		Not statistically significant: Postnatal marijuana use: 10/233 vs 11/234 § aOR: 0.60, 95%CI [0.2;1.8] ¥ (p=0.42)	1, 233 vs 234	Klonoff-Cohen, 2001
		Not statistically significant: Maternal cannabis use since birth: 79/393 vs 113/1586 § aOR: 1.38, 95%CI [0.90;2.12] ¥ (p>0.05)	1, 393 vs 1586	Scragg, 2001
		Not statistically significant: Maternal other illicit drug use since birth: 9/393 vs 5/1587 § aOR: 1.37, 95%CI [0.31;6.12] ¥ (p>0.05)	1, 393 vs 1587	

* Calculations done by the reviewer(s) using Review Manager software

£ No raw data available

¥ Imprecision (large variability of results)

§ Imprecision (low number of events)

Quality of evidence

Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations
Alm, 1999	No, controls were gender, age, data of birth plus 2 weeks and maternity hospital matched.	Unclear, not clear if autopsy was performed to confirm SIDS.	No, aOR adjusted for maternal age, education, smoking and paternal unemployment.	No	Plausibility of prenatal alcohol or drugs effect, since mothers who consumed alcohol or used drugs during pregnancy were very likely to consume alcohol or use drugs postnatally.
Blair, 1996	Controls matched for age and date of interview.	No, only those infants included that died from SIDS validated by full postmortem examination.	No, aOR adjusted for smoking.	No	
Blair, 2009	No, controls matched for age and time of day	No, SIDS confirmed by full pedriatic autopsy.	No, adjusted for infant's age and daytime or night time sleep,	No	

	of the reference sleep.		maternal smoking during pregnancy, maternal social class, young maternal age, and ≥3 live births as well as other significant factors in multivariable model		
Carpenter, 2004	No, controls matched for age and living area.	No, only cases with full autopsy were included.	No, aOR adjusted for age and centres.	No	
Carpenter, 2013	No, controls were randomly selected, normal infants of similar age, time and place.	No, SIDS were included by standard criteria.	No, adjusted for age, study and bed sharing	No, missing data were imputed	Missing records for alcohol comsumption 61.3% and for drug use 60.5%.
Klonoff-Cohen, 2001	No, controls were matched for birth hospital, date of birth, age and gender.	No, diagnosis of SID confirmed by autopsy	No, aOR adjusted for smoking and drinking during pregnancy, maternal, age and level of education, low infant birth weight, infant medical condition at birth, infant sleeping position and bed sharing.	No	Possible recall bias as telephone interviews were conducted 6-12 months after infants death.
L'hoir, 1998	No, controls were matched for date of birth.	No, diagnosis of SID confirmed by autopsy, excluded major pathological abnormalities	No, adjusted for age, sleeping position, duvet use, use of sleeping sack, dummy use.	No	
Scragg, 1993, New Zealand	No, controls were age matched.	No, autopsy in 97.8% SIDS.	aOR adjusted for ethnic origin.	No	
Scragg, 2001, New Zealand	No, controls were matched for age.	Unclear, not clear if autopsy was performed to confirm SID.	No, aOR adjusted for etnicity, tobacco or cannabis, adjusted for main confounders	No	

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	low number of events/large variability of results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Very Low [D]**	

Conclusion	**Alcohol use** There is limited evidence with harm for postnatal maternal alcohol consumption. It was shown that postnatal alcohol consumption (in the last 24 h or in the last month) resulted in a statistically significant increased risk of sudden infant death syndrome (Blair 1996, Blair 2009, Carpenter 2004, carpenter 2013, L'Hoir 1998, Scragg 1999). A statistically significant increased risk of SIDS in case of maternal alcohol use less than weekly or more than weekly could not be demonstrated (Alm, 1999). Evidence is of very low quality and results cannot be considered precise due to low number of events and/or large variability of results. **Drug use** There is limited evidence with harm for postnatal maternal drug use. It was shown that postnatal drug use resulted in a statistically significant increased risk of sudden infant death syndrome (Blair 1996, Carpenter 2004, Carpenter 2013). A statistically significant increased risk of SIDS in case of maternal marijuana or other illicit drug use could not be demonstrated (Blair 2009, Klonoff-Cohen 2001, Scragg 2001). Evidence is of very low quality and results cannot be considered precise due to low number of events and/or large variability of results. There is a plausibility of prenatal alcohol or drugs effect, since mothers who consumed alcohol or used drugs during pregnancy were very likely to consume alcohol or use drugs postnatally.
Reference(s)	**Articles** Alm B, Wennergren G, Norvenius G,Skjaerven R, Oyen N, Helweg-Larsen K, Lagercrantz H, Irgens LM. *Caffeine and alcohol as risk factors for sudden infant death syndrome. Nordic Epidemiological SIDS Study.* Arch dis Child 81 (2):107-111. Blair PS, Fleming PJ, Bensley D, Smith I, Bacon C, Taylor E, Berry J, Golding J, Tripp J. *Smoking and the sudden infant death syndrome: results from 1993-5 case-control study for confidential inquiry into stillbirths and deaths in infancy. Confidential Enquiry into Stillbirths and Deaths Regional Coordinators and Researchers.* BMJ 1996; 313(7051):195-198. Blair PS, Sidebotham P, Evason-Coombe C, Edmonds M, Heckstall-Smith EM, Fleming P. *Hazardous cosleeping environments and risk factors amenable to change: case-control study of SIDS in south west England*. BMJ 2009; 339:b3666. Carpenter RG, Irgens LM, Blair PS, England PD, Fleming P, Huber J, Jorch G, Schreuder P. *Sudden unexplained infant death in 20 regions in Europe: case control study.* Lancet 2004; 363(9404):185-191. Carpenter R, McGarvey C, Mitchell EA, Tappin DM, Vennemann MM, Smuk M, Carpenter JR. *Bed sharing when parents do not smoke: is there a risk of SIDS? An individual level analysis of five major case-control studies*. BMJ Open 2013; 3(5). Klonoff-Cohen H, Lam-Kruglick P. Maternal and paternal recreational drug use and sudden infant death syndrome. *Arch Pediatr Adolesc Med* 2001; 155(7):765-770. L'hoir MP, Engelberts AC, van Well GT, Westers P, Mellenbergh GJ, Wolters WH, Huber J. Case-control study of current validity of previously described risk factors for SIDS in The Netherlands. *Arch Dis Child* 1998; 79(5):386-393. Scragg R, Mitchell EA, Taylor BJ, Stewart AW, Ford RP, Thompson JM, Allen DMO. Bed sharing, smoking, and alcohol in the sudden infant death syndrome. New Zealand Cot Death Study Group. *BMJ* 1993; 307(6915):1312-1318. Scragg RK, Mitchell EA, Ford RP, Thompson JM, Taylor BJ, Stewart AW. Maternal cannabis use in the sudden death syndrome. *Acta Paediatr* 2001; 90(1):57-60.

Sudden infant death syndrome (SIDS) – Sleep monitoring (Diagnostics)

Question (PICO)	In babies (P), should polysomnography (I) be used to diagnose sudden infant death syndrome (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh sudden infant death] OR "sudden infant death":ti,ab,kw OR "SID":ti,ab,kw OR "SIDS":ti,ab,kw OR "Crib death":ti,ab,kw OR "Cot death":ti,ab,kw 2. [mh polysomnography] OR "Polysomnography":ti,ab,kw OR "Polysomnographies":ti,ab,kw OR "Somnography":ti,ab,kw OR "Somnographies":ti,ab,kw OR "sleep monitoring":ti,ab,kw 3. [mh sensitivity and specificity] OR "Sensitivity":ti,ab,kw OR "Specificity":ti,ab,kw OR "Pre-test probability":ti,ab,kw OR "Pretest probability":ti,ab,kw OR "Post-test probability":ti,ab,kw OR "Posttest probability":ti,ab,kw OR "Predictive value":ti,ab,kw OR "Predictive values":ti,ab,kw OR "Likelihood ratio":ti,ab,kw OR "Likelihood ratios":ti,ab,kw 4. 1-3 AND **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Sudden infant death"[Mesh] OR "sudden infant death"[TIAB] OR "SID"[TIAB] OR "SIDS"[TIAB] OR "Crib death"[TIAB] OR "Cot death"[TIAB] 2. "Polysomnography"[Mesh] OR "Polysomnography"[TIAB] OR "Polysomnographies"[TIAB] OR "Somnography"[TIAB] OR "Somnographies"[TIAB] OR "sleep monitoring"[TIAB] 3. "Sensitivity and specificity"[Mesh] OR "Sensitivity"[TIAB] OR "Specificity"[TIAB] OR "Pre-test probability"[TIAB] OR "Pretest probability"[TIAB] OR "Post-test probability"[TIAB] OR "Posttest probability"[TIAB] OR "Predictive value"[TIAB] OR "Predictive values"[TIAB] OR "Likelihood ratio"[TIAB] OR "Likelihood ratios"[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'Sudden infant death'/exp OR 'sudden infant death':ab,ti OR 'SID':ab,ti OR 'SIDS':ab,ti OR "Crib death":ab,ti OR "Cot death":ab,ti 2. 'Polysomnography'/exp OR 'Polysomnography':ab,ti OR 'Polysomnographies':ab,ti OR 'Somnography':ab,ti OR 'Somnographies':ab,ti OR 'sleep monitoring':ab,ti 3. 'Diagnostic accuracy'/exp OR 'Sensitivity and specificity'/exp OR 'Sensitivity':ab,ti OR 'Specificity':ab,ti OR ((Pre-test or pretest) near/5 probability):ab,ti OR 'Post-test probability':ab,ti OR 'Posttest probability':ab,ti OR 'Predictive value':ab,ti OR 'Predictive values':ab,ti OR 'Likelihood ratio':ab,ti OR 'Likelihood ratios':ab,ti 4. 1-3 AND
Search date	15 July 2015
In/Exclusion criteria	**Population:** Include: infants **Intervention:** Include: sleep monitoring **Comparison:** Include: a diagnostic reference method for the diagnosis of sudden infant death syndrome Exclude: studies not using a diagnostic reference method. **Outcome:** Include: Patient-important outcomes (i.e. survival) or accuracy-related outcomes such as sensitivity, specificity and/or positive/negative likelihood ratio (pLR/nLR). Likelihood ratios were considered as the preferred measure of diagnostic accuracy since they are clinically more meaningful than sensitivities, specificities, or diagnostic odds ratios. They quantify how strongly the likelihood of a disease is changed by the presence (pLR) or absence (nLR) of a symptom or sign. A LR of 1 indicates a test result without any diagnostic value. LRs of 1 to 2 or 0.5 to 1 change the likelihood very little and they are rarely important. LRs ≤0.5 or ≥2 change it at least moderately and can be considered as clinically helpful in the context of medical history taking and physical

	examination. If no information on likelihood ratios is reported, data of sensitivity and specificity are extracted. **Study design:** Include: a systematic review (of diagnostic accuracy studies) was included if the search strategy and selection criteria are clearly described and if at least MEDLINE and one other relevant database was searched. If no systematic review was published within the last 5 years, individual experimental, observational and/or diagnostic accuracy studies were included. Exclude: case series**,** animal studies, *ex vivo* or *in vitro* studies. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline)

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Sudden infant death syndrome (SIDS) – Vaccination (Risk Factor)

Question (PICO)	In infants (P), is vaccination (RF), compared to no vaccination (C) a risk factor for SIDS (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "sudden infant death"] OR "sudden infant death":ti,ab,kw OR "sudden infant death syndrome":ti,ab,kw OR "SID":ti,ab,kw OR "SIDS":ti,ab,kw OR (crib NEXT death*):ti,ab,kw OR (cot NEXT death*):ti,ab,kw OR (unexpected infant NEXT death*):ti,ab,kw 2. [mh "vaccination"] OR [mh "vaccines"] OR vaccin*:ti,ab,kw OR (active NEXT immunization*):ti,ab,kw OR (active NEXT immunisation*):ti,ab,kw OR immunisation*:ti,ab,kw OR immunization*:ti,ab,kw 3. #1 AND #2 **MEDLINE** (via PubMed interface) for systematic reviews, experimental and observational studies using the following search strategy: 1. "Sudden infant death"[MeSH] OR "sudden infant death"[TIAB] OR "sudden infant death syndrome"[TIAB] OR SID[TIAB] OR SIDS[TIAB] OR crib death*[TIAB] OR cot death*[TIAB] OR unexpected infant death*[TIAB] 2. "vaccination"[MeSH] OR "vaccines"[MeSH] OR vaccin*[TIAB] OR active immunization*[TIAB] OR active immunization*[TIAB] OR immunization*[TIAB] OR immunization*[TIAB] 3. #1 AND #2 **Embase** (via Embase.com interface) using the following search strategy:

	1. 'sudden infant death syndrome'/exp OR 'sudden infant death':ab,ti OR 'sudden infant death syndrome':ab,ti OR (crib NEXT/1 death*):ab,ti OR (cot NEXT/1 death*):ab,ti OR (unexpected infant NEXT/1 death*):ab,ti 2. 'vaccination'/exp OR 'vaccine'/exp OR vaccin*:ab,ti OR (active NEXT/1 immunization*):ab,ti OR (active NEXT/1 immunisation*):ab,ti OR immunization*:ab,ti OR immunisation*:ab,ti 3. #1 AND #2 Meta-analysis retrieved with the above searches, and used as source for individual studies: Vennemann, 2007b Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	28 January 2016
In/Exclusion criteria	**Population:** Include: Infants of < 2 years old. Exclude: Infants of > 2 years old. **Intervention:** Include: Vaccination Exclude: Any other intervention. **Comparison:** Include: No vaccination **Outcome:** Include: SIDS **Study design:** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: observational studies if intervention is already included in experimental studies, case series, cross-sectional studies, animal studies, ex vivo or in vitro studies, conference abstracts, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Risk factor	Remarks
Bouvier-Colle, 1989, France	Observational: Case-control study	Infants, 135 cases vs 401 controls, 84 days old	Being DTP-vaccinated, defined as having received the first dose of the DTP vaccine, vs not being DTP-vaccinated	Data were obtained through a doctor's questionnaire (cases) or a governmental service (controls)
Fleming, 2001, UK	Observational: Case-control study	Infants, 303 cases vs 1234 controls, aged 1 week to 1 year.	Being vaccinated, defined as having received any component of the vaccination scheme before death/reference sleep, vs not being vaccinated.	Parents were interviewed via a questionnaire. Vaccination information was obtained from health records kept by parents.
Hoffman, 1987, USA	Observational: Case-control study	Infants, 757 cases vs 1514 controls, aged 14 days to 24 months.	Being vaccinated with the DTP-vaccine vs not being vaccinated with the DTP-vaccine.	Parents were interviewed via a questionnaire. Vaccination information was

			Being vaccinated with the oral polio-vaccine vs not being vaccinated with the oral polio-vaccine.	obtained from health records and the parent's questionnaire simultaneously.
Jonville-Bera, 1995, France	Observational: Case-control study	Infants, 118 cases vs 332 controls, average age at death 3 months and 10 days ± 2months and 26 days	Being vaccinated with at least one dose of DTP+ polio vs not being vaccinated with at least one dose of DTP+polio.	Fashion of data collection was not clearly stated. Only a minority of the cases were confirmed by autopsy.
Jonville-Bera, 2001, France	Observational: Case-control study	Infants, 114 cases and 341 controls, aged 30 days to 90 days.	Being vaccinated with at least one dose of DTP, polio with or without heamophilus influenza vaccine vs not being vaccinated with at least one dose of DTP, polio with or without heamophilus influenza vaccine.	Parents were interviewed via a questionnaire. Vaccination information was obtained from health records.
Mitchell, 1995, New Zealand	Observational: Case-control study	Infants, 317 cases and 1524 controls.	Being vaccinated, defined as received any vaccination dose due at the given age vs not being vaccinated. This was examined at birth, 6 weeks, 3 months and 5 months (time points were children are vaccinated according to the New Zealand vaccination programme).	Parents were interviewed via a questionnaire. Vaccination information was obtained from health records kept by parents.
Vennemann, 2007a, Germany	Observational: Case-control study	Infants, 307 cases and 971 controls.	Being vaccinated with any type of vaccine vs not being vaccinated, subdivided by age at time of death (<2, 3, 4, 5 and >6 months) and in total. Being vaccinated within 14 days vs not being vaccinated within 14 days. Being vaccinated with the hexavalent vaccines vs not being vaccinated. [Only data from vaccinated vs not vaccinated in total and being vaccinated with hexavalent vaccines vs not being vaccinated was extracted]	Parents were interviewed via a questionnaire. Vaccination information was obtained from health records.
Walker, 1987, USA	Observational: Case-control study	Infants with birth weight >2.5 kg, 29 cases and unknown # controls, aged 30-365 days.	Being vaccinated with DTP vs not being vaccinated with DTP.	Vaccination information was obtained from health records.

Synthesis of findings

Outcome	Risk factor	Effect Size	#studies, # participants	Reference
Prevalence of SIDS	Vaccinated with DTP vaccine vs not vaccinated with DTP vaccine	Not statistically significant: OR: 0.76, 95%CI[0.51-1.13]* ¥ (p>0.05)	1, 135 vs 401 §	Bouvier-Colle, 1989
	Vaccinated vs not vaccinated	Not statistically significant: 149/303 vs 822/1234 aOR: 0.67, 95%CI[0.31-1.43] ¥ (p>0.05)	1, 303 vs 1234	Fleming, 2001
	Vaccinated with DTP-vaccine vs not vaccinated with DTP-vaccine	Statistically significant: 285/716 vs 416/757 aOR: 0.7 £ (p=0.003) *With beneficiary effect of DTP vaccination*	1, 716 vs 757	Hoffman, 1987
	Vaccinated with oral polio-vaccine vs not vaccinated with oral polio-vaccine	Statistically significant: 283/717 vs 405/757 OR: 0.57, 95%CI[0.46-0.7]* (p<0.05) *With beneficary effect of oral polio vaccination*	1, 717 vs 757	
	Vaccinated with DTPP-vaccine vs not vaccinated with DTPP-vaccine	Not statistically significant: 38/118 vs 90/332 OR: 1.9, 95%CI[0.9-3.9] ¥ (p>0.05)	1, 118 vs 332 §	Jonville-Bera, 1995
	Vaccinated with DTPP±Hib vs not vaccinated with DTPP±Hib	Not statistically significant: 14/114 vs 47/341 aOR: 1.08, 95%CI[0.49-2.36] ¥ (p>0.05)	1, 114 vs 341 §	Jonville-Bera, 2001
	Vaccinated vs not vaccinated at birth	Not statistically significant: 219/317 vs 1000/1524 aOR: 1.1, 95%CI[0.8-1.6] ¥ (p>0.05)	1, 317 vs 1524	Mitchell, 1995
	Vaccinated vs not vaccinated at 6 weeks	Statistically significant: 233/279 vs 1256/1373 aOR: 2.1, 95%CI[1.2-3.5] (p<0.05) *With beneficiary effect of vaccination*		
	Vaccinated vs not vaccinated at 3 months	Not statistically significant: 103/143 vs 674/777 aOR: 1.3, 95%CI[0.7-2.5] ¥ (p>0.05)		
	Vaccinated vs not vaccinated at 5 months	Not statistically significant: 31/50 vs 259/338 aOR: 2.6, 95%CI[0.9-7.5] ¥ (p>0.05)		
	Vaccinated vs not vaccinated	Not statistically significant: 154/307 vs 585/971 aOR: 0.51, 95%CI[0.25-1] ¥ (p>0.05)	1, 307 vs 971	Vennemann, 2007a
	Vaccinated with hexavalent vaccine vs not vaccinated with hexavalent vaccine	Not statistically significant: 22/127 vs 100/278 aOR: 0.77, 95%CI[0.26-2.24] ¥ (p>0.05)	1, 127 vs 278	

	DTP vaccinated vs not DTP vaccinated	Statistically significant: aOR: 6.5, 95%CI[2.2-19] (p<0.05) ££ *With beneficiary effect of vaccination with DTP*	1, 29 vs unknown †	Walker, 1987

Mean ± SD (unless otherwise indicated)
* Calculations done by the reviewer(s) using Review Manager software
£ No CI available
££ No raw data available
¥ Imprecision (large variability of results)
† Imprecision (lack of data)
§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations
Bouvier-Colle, 1989	Yes, children were considered SIDS based on doctor's records, but not autopsy. In addition, also children whose death was classified as "due to inhalation and ingestion of food causing obstruction of the respiratory tract or suffocation" were included.	Yes, immunization status was verified in a different manner for cases and controls.	Yes, controls were age- and gender-matched, but no other factors were taken into account in the analysis (univariate OR).	No	
Fleming, 2001	No	Yes, information about vaccination was obtained from parents, not health care provider or official records	No, controlled for age, socioeconomic status, moved house in the last year, parity, maternal age, birth weight, gestational age, admitted to special care unit, admitted to hospital, 5 min APGAR score, apparent life threatening events, sleeping position, found with bedclothes over head.	No	
Hoffman, 1987	No	No	Yes, controls were age-, birth weight- and age-matched, but other important factors were not taken into account in the analysis (e.g. prone position).	No	

Jonville-Bera, 1995	Yes, children were mostly considered SIDS based on doctor's records while only 28% was confirmed by autopsy.	Unclear, not stated how vaccination data was obtained	Yes, controls were age- and gender-matched, but no other factors were taken into account in the analysis (univariate OR).	No	
Jonville-Bera, 2001	No	No	No, controlled for sleeping position, birth weight, illness week before death, matress type, maternal smoking, sex, breastfeeding.	Yes, study early terminated due to funding issues	
Mitchell, 1995	No	Yes, information about vaccination was obtained from parent-held records	No, controlled for marital status, occupation, age mother left school, age of mother, parity, age at first pregnancy, late attendance at antenatal clinic, antenatal education classes attended, ethnicity, sex, birth weight, gestation, region, season, breastfeeding, admission of special care or neonatal intensive care baby units, age of infant, infant taken to child health nurse clinic, maternal smoking, sleep position, bed sharing, infection.	No	
Vennemann, 2007a	No	No	No, controlled for maternal age at delivery, family status, smoking of the mother in pregnancy, parity, socio-economic status, birth weight, breastfeeding, pillow in the bed, position placed to sleep, pacifier, and infant sharing a bed with an adult.	No	
Walker, 1987	No	No	Yes, multivariate OR only accounts for age and study period.	No	

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	4/8 studies have low # events, 6/8 studies have large variability in results, 1/8 studies has lack of data
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Conclusion	There is limited evidence with benefit for vaccination: It was shown that vaccination resulted in a statistically significant decreased risk of sudden infant death syndrome, compared to no vaccination (Hoffman 1987, Mitchell 1995, Walker 1987). Evidence is of very low quality and results cannot be considered precise due to limited sample size, lack of data and/or large variability of results. There is limited evidence neither for the benefit of vaccination nor no vaccination: A statistically significant decreased risk of sudden infant death syndrome in case of vaccination compared to no vaccination could not be demonstrated (Bouvier-Colle 1989, Fleming 2001, Jonville-Bera 1995, Jonville-Bera 2001, Mitchell 1995, Vennemann 2007a). Evidence is of very low quality and results cannot be considered precise due to limited sample size and/or large variability of results.
Reference(s)	**Articles** Bouvier-Colle MH, Flahaut A, Messiah A, Jougla E, Hatton F. Sudden infant death and immunization: an extensive epidemiological approach to the problem in France--winter 1986. Int J Epidemiol. 1989 Mar;18(1):121-6. Fleming PJ, Blair PS, Platt MW, Tripp J, Smith IJ, Golding J. *The UK accelerated immunisation programme and sudden unexpected death in infancy: case-control study.* BMJ. 2001 Apr 7;322(7290):822. Hoffman HJ, Hunter JC, Damus K, Pakter J, Peterson DR, van Belle G, Hasselmeyer EG. *Diphtheria-tetanus-pertussis immunization and sudden infant death: results of the National Institute of Child Health and Human Development Cooperative Epidemiological Study of Sudden Infant Death Syndrome risk factors.* Pediatrics. 1987 Apr;79(4):598-611. Jonville-Bera AP, Autret E, Laugier J. *Sudden infant death syndrome and diphtheria-tetanus-pertussis-poliomyelitis vaccination status.* Fundam Clin Pharmacol. 1995;9(3):263-70. Jonville-Béra AP, Autret-Leca E, Barbeillon F, Paris-Llado J; French Reference Centers for SIDS. *Sudden unexpected death in infants under 3 months of age and vaccination status- -a case-control study.* Br J Clin Pharmacol. 2001 Mar;51(3):271-6. Mitchell EA, Stewart AW, Clements M. *Immunisation and the sudden infant death syndrome. New Zealand Cot Death Study Group.* Arch Dis Child. 1995 Dec;73(6):498-501. Vennemann MM, Butterfass-Bahloul T, Jorch G, Brinkmann B, Findeisen M, Sauerland C, Bajanowski T, Mitchell EA; GeSID Group. *Sudden infant death syndrome: no increased risk after immunisation.* Vaccine. 2007 Jan 4;25(2):336-40. Vennemann MMT, Höffgen M, Bajanowski T, Hense H, Mitchell EA. *Do immunisations reduce the risk for SIDS? A meta-analysis.* Vaccine. 2007; 25: 4875–4879 Walker AM, Jick H, Perera DR, Thompson RS, Knauss TA. *Diphtheria-tetanus-pertussis immunization and sudden infant death syndrome.* Am J Public Health. 1987 Aug;77(8):945-51.

PRIMARY ASSESSMENT AND TRANSPORTATION OF A CASUALTY

Emergency triage and treatment – ABCDE Approach

Question (PICO)	In a seriously injured or unconscious person (P), is the ABCDE approach (I) effective for primary assessment (O) compared to another approach (C)?
Search Strategy	Databases **GIN, NGC, WHO** (guidelines) using the search terms 'ETAT' OR 'Emergency triage and treatment ' OR 'victim approach' OR 'primary assessment' OR 'initial assessment and treatment' OR 'ABCDE' OR 'Airway, Breathing, Circulation, Disability, Exposure' **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. ("Emergency triage and treatment"):ti,ab,kw OR ("victim approach"):ti,ab,kw OR ("primary assessment"):ti,ab,kw OR ("initial assessment and treatment"):ti,ab,kw 2. ("ABCDE"):ti,ab,kw OR ("Airway, Breathing, Circulation, Disability, Exposure"):ti,ab,kw 3. #1 or #2 **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Emergency triage assessment"[TIAB] OR "victim approach"[TIAB] OR "primary assessment"[TIAB] OR ("initial assessment" AND "emergency triage") OR ("ETAT" AND "emergency") 2. "ABCDE"[TIAB] OR (Airway AND Breathing AND Circulation AND Disability AND Exposure) 3. 1-2 OR **Embase** (via Embase.com interface) using the following search strategy: 1. 'Emergency triage assessment':ab:ti OR 'victim approach':ab:ti OR 'primary assessment':ab:ti OR ('initial assessment':ab,ti AND 'emergency triage':ab:ti) 2. 'ABCDE':ab:ti OR ('Airway':ab:ti AND 'Breathing':ab:ti AND 'Circulation':ab:ti AND 'Disability':ab:ti AND 'Exposure':ab:ti) 3. 1-2 OR
Search date	12 February 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available.

	An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies. **Language**: Include: English **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Emergency triage and treatment – Safety, stimulate, shout (SSS)

Question (PICO)	In a seriously injured or unconscious person (P), is the SSS approach (I) effective for primary assessment (O) compared to another approach (C)?
Search Strategy	Databases **GIN, NGC, WHO** (guidelines) using the search terms 'ETAT' OR 'Emergency triage and treatment ' OR 'victim approach' OR 'primary assessment' OR 'Safety, stimulate, shout' **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. ("Emergency triage and treatment"):ti,ab,kw OR ("victim approach"):ti,ab,kw OR ("primary assessment"):ti,ab,kw OR ("initial assessment and treatment"):ti,ab,kw 2. ("Safety, stimulate, shout"):ti,ab,kw OR ("SSS"):ti,ab,kw 3. #1 or #2 **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Emergency triage assessment"[TIAB] OR "victim approach"[TIAB] OR "primary assessment"[TIAB] OR ("initial assessment" AND "emergency triage") 2. "SSS"[TIAB] AND ("Safety" [TIAB] OR "stimulate"[TIAB] OR "shout"[TIAB]) 3. 1-2 OR **Embase** (via Embase.com interface) using the following search strategy: 1. 'Emergency triage and treatment':ab:ti OR 'victim approach':ab:ti OR 'primary assessment':ab:ti OR ('initial assessment':ab,ti AND 'emergency triage':ab:ti) 2. 'SSS':ab:ti AND ('Safety':ab:ti OR 'stimulate':ab:ti OR 'shout':ab:ti) 3. 1-2 OR
Search date	12 February 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare.

	Outcome: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies. **Language**: Include: English **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Trauma Severity Index – AVPU scale

Question (PICO)	In a seriously injured or unconscious person (P), is the AVPU scale (I) effective for primary assessment (O) compared to another approach (C)?
Search Strategy	Databases **GIN, NGC, WHO** (guidelines) using the search terms 'AVPU' OR 'Trauma Severity Indices' OR 'alert, verbal, painful, unresponsiveness' **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Trauma Severity Indices"] and (("alert"):ti,ab,kw or ("verbal"):ti,ab,kw or ("painful"):ti,ab,kw or ("unresponsiveness"):ti,ab,kw) 2. ("AVPU"):ti,ab,kw or ("alert, verbal, painful, unresponsiveness"):ti,ab,kw 3. #1 or #2 **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Trauma Severity Indices "[Mesh] AND ("alert"[TIAB] OR "verbal"[TIAB] OR "painful"[TIAB] or "unresponsiveness"[TIAB]) 2. "AVPU"[TIAB] OR ("alert" AND "verbal" AND "painful" AND "unresponsiveness") 3. 1-2 OR **Embase** (via Embase.com interface) using the following search strategy: 1. 'injury scale'/exp AND ('alert':ab:ti OR 'verbal':ab:ti OR 'painful':ab:ti or 'unresponsiveness':ab:ti) 2. 'AVPU':ab:ti OR 'alert, verbal, painful, unresponsiveness':ab:ti 3. 1-2 OR

Search date	13 February 2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. Interventions done by healthcare professionals in hospital settings. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies. **Language**: Include: English **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Primary assessment – AVPU scale (Feasibility)

Question (PICO)	In humans (P), is the AVPU scale used by laypeople (I) compared to the AVPU scale used by professionals (C) more correct for primary assessment (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: "AVPU":ti,ab,kw OR (alert:ti,ab,kw AND verbal:ti,ab,kw AND pain*:ti,ab,kw AND unresponsive*:ti,ab,kw) **MEDLINE** (via PubMed interface) using the following search strategy: AVPU[TIAB] OR (alert[TIAB] AND verbal[TIAB] AND pain*[TIAB] AND unresponsive*[TIAB]) **Embase** (via Embase.com interface) using the following search strategy: 'AVPU':ab,ti OR (alert:ab,ti AND verbal:ab,ti AND pain*:ab,ti AND unresponsive*:ab,ti)

Search date	25 August 2015
In/Exclusion criteria	**Population**: Include: Healthy volunteers of all ages. **Intervention**: Include: AVPU assessment performed by lay people (i.e. basic first responders, lay caregivers and/or community health workers). **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies. **Language**: Include: English **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Critical injury – START principle (Diagnostics)

Question (PICO)	In humans (P), is triage with START-principle (I) compared to another test (C) effective to identify critical patients (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. START:ti,ab,kw OR (simple:ti,ab,kw AND triage:ti,ab,kw AND rapid:ti,ab,kw AND treatment:ti,ab,kw) 2. [mh "patient transfer"] OR transfer*:ti,ab,kw OR [mh triage] OR triage:ti,ab,kw OR [mh checklist] 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental, observational and/or diagnostic accuracy studies using the following search strategy: 1. simple[TIAB] AND triage[TIAB] AND rapid[TIAB] AND treatment[TIAB] 2. "Patient transfer"[Mesh] OR transfer*[TIAB] OR handover[TIAB] OR triage[Mesh] OR triage[TIAB] OR checklist[Mesh] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy:

	1. simple:ab,ti AND triage:ab,ti AND rapid:ab,ti AND treatment:ab,ti 2. 'patient transport'/exp OR transfer*:ab,ti OR handover:ab,ti OR 'emergency health service'/exp OR triage:ab,ti OR checklist/exp 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in MEDLINE (via PubMed interface).
Search date	17 July 2015
In/Exclusion criteria	**Population** Include: Adults and children with trauma **Intervention** Include: Triage performed with START (Simple Triage and Rapid Treatment) **Comparison** Include: Index test for critical injury: injury severity score (ISS), probability of survival. Triage performed with other methods such as First Impression Triage (FIT) **Outcome** Include: Diagnostic related outcomes such as sensitivity, specificity, AUC (area under curve), positive/negative likelihood ratio (PLR/NLR). PLR=sensitivity/(1-specificity); NLR=(1-sensitivity)/specificity. Likelihood ratios were considered as the preferred measure of diagnostic accuracy since they are clinically more meaningful than sensitivities, specificities, or diagnostic odds ratios. They quantify how strongly the likelihood of a disease is changed by the presence (pLR) or absence (nLR) of a symptom or sign. A LR of 1 indicates a test result without any diagnostic value. LRs of 1 to 2 or 0.5 to 1 change the likelihood very little and they are rarely important. LRs ≤0.5 or ≥2 change it at least moderately and can be considered as clinically helpful in the context of medical history taking and physical examination (Furukawa, et al 2008*). Only positive likelihood ratios will be extracted (if present) because the effectiveness/clinical relevance of identifying critically ill patients with a positive test (pLR) is of higher value than the effectiveness/clinical relevance of identifying critically ill patients with a negative test (nLR). If only AUC is mentioned, a comparison between two scores should be made and a p-value or narrative description of significance should be mentioned. In case a statistical comparison is made between to triage methods and a p-value is mentioned, a conclusion will be made in favour of a test (if statistically significant). If no p-values are mentioned, and only likelihood ratios are mentioned or calculated, a conclusion will be made on the clinical relevance of the triage method based on the above mentioned cut-off values. **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study (accuracy study): inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

* Furukawa TA, Strauss S, Bucher HC, Guyatt G. Diagnostic tests. In: Guyatt G, Rennie D, Meade MO, Cook DJ, editors. Users' guides to the medical literature A manual for evidence-based clinical practice. 2nd ed. New York: McGraw Hill Medical; 2008.p. 419-38.

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Hashimoto, 2013, Japan	Diagnostics: diagnostic accuracy study	113 victims of a train derailing who were transported to the Hospital of Hyogo College of Medicine. On patient's arrival, triage was performed with FIT. After transferring to a designated area, patients were reassessed with the modified START.	1. Modified START vs ISS≥15 2. Modified START vs Ps 3. Modified START vs FIT	Ps = probability of survival. ISS = Injury Severity Score
Wallis, 2006, UK	Diagnostics: diagnostic accuracy study	3461 children <13 years (63% male, median age 7 years) presenting at Trauma Unit of the Red Cross Children's Hospital, Cape Town within 12 hours after acute injury. Performance of scores were defined against their ability to discriminate between T1 (immediate priority) and not-T1 (urgent or delayed priority). Children were considered seriously injured (=T1) if ISS>15. Children with ISS≤15 were considered not-T1.	1. START (8-13 years) vs ISS 2. JumpSTART (1-8 years) vs ISS	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Adults				
Critical injury	Modified START vs ISS≥15	Sensitivity: 50.0% Specificity: 96.4% PLR: 13.9 *† *START can be considered as clinically helpful for the triage of critically ill patients*	1, 113 § (diagnostic accuracy study)	Hashimoto, 2013
	Modified START vs Ps	Sensitivity: 60.0% Specificity: 93.9% PLR: 9.84 *† *START can be considered as clinically helpful for the triage of critically ill patients*		
Injury Severity Score (ISS) ≥15	Modified START vs FIT	Statistically significant: Accuracy rate: 84.2% vs 68.4% p<0.05 † *In favour of Modified START*		
Probability of survival	Modified START vs FIT	Not statistically significant: Accuracy rate: 89.5% vs 81.6% p>0.05 †		
Children				
Injury Severity Score (ISS)>15	START vs ISS>15	Sensitivity: 31.3%, 95%CI [21.5; 42.8] Specificity: 77.9%, 95%CI [77.3; 78.7] PLR: 1.42 *† *START can be considered as not clinically helpful for the triage of critically ill paediatric patients*	1, 1020 (diagnostic accuracy study)	Wallis, 2006

	JumpSTART vs ISS>15	Sensitivity: 3.2%, 95%CI [1.3; 7.5] Specificity: 97.8%, 95%CI [97.7; 98.0] PLR: 1.45 *† *JumpSTART can be considered as <u>not</u> clinically helpful for the triage of critically ill paediatric patients*	1, 2441 (diagnostic accuracy study)	

† Imprecision (lack of data)

§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Could the selection of patients have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?	Could the reference standard, its conduct, or its interpretation have introduced bias?	Could the patient flow have introduced bias?	Other limitations
Hashimoto, 2013	No, patients were admitted after disaster	No	No	Unclear	
Wallis, 2006	No	No	No	Yes, the regular recording of the triage score criteria over a period of months may have led to a much greater degree of familiarity with the methods than could be expected in a real incident.	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Lack of data
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	<u>Adult patients</u>: There is limited evidence in favour of Modified START for the triage of critically injured patients. It was shown that Modified START resulted in a statistically significant increased identification of patients with an injury severity score >15, compared to FIT. However, a statistically significant increased indication of probability of survival, using Modified START compared to FIT, could not be demonstrated (Hashimoto 2013). Additionally, Modified START can be considered as clinically helpful for the triage of critically injured patients. Evidence is of low quality and results of this study are imprecise due to lack of data. <u>Paediatric patients</u>: There is limited evidence showing that Modified START or JumpSTART cannot be considered as clinically helpful for the triage of critically ill children (Wallis 2006). Evidence is of low quality and results of this study are imprecise due to lack of data.

Reference(s)	**Articles** Hashimoto A, Ueda T, Kuboyama K, Yamada T, Terashima M, Miyawaki A, Nakao A, Kotani J. *Application of a First Impression Triage in the Japan Railway West Disaster*. Acta Med Okayama 2013, 67(3):171-176 Wallis LA, Carley S. *Comparison of paediatric major incident primary triage tools*. Emerg Med J 2006, 23:475-478

Diagnosing at-risk patients – Early Warning Score (Diagnostics)

Question (PICO)	In humans (P), is the use of the Early Warning Score (EWS) (I) compared to no or another scoring system (C) effective to identify at-risk patients (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: "Early warning":ti,ab,kw AND (score:ti,ab,kw OR scoring:ti,ab,kw) OR EWS:ti,ab,kw **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "early warning"[TIAB] AND (score[TIAB] OR scoring[TIAB]) OR EWS[TIAB] 2. illness[TIAB] OR deterioration[TIAB] OR at-risk[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'early warning':ab,ti AND (score:ab,ti OR scoring:ab,ti) OR EWS:ab,ti 2. 'general condition deterioration'/exp OR deterioration/exp OR illness:ab,ti OR deterioration:ab,ti OR at-risk:ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	12 August 2015
In/Exclusion criteria	**Population**: Include: adult medical patients. Exclude: neonates and children **Intervention**: Include: Early Warning Score, or its modified forms, such as Modified Early Warning Score (MEWS), National Early Warning Score (NEWS) or Scottish Early Warning Score (SEWS). **Comparison**: Include: acute admission; other scoring systems such as Patient at Risk Score (PARS) or Rapid Emergency Medicine Score (REMS). **Outcome**: Include: Include: Diagnostic related outcomes such as sensitivity, specificity, AUC (area under curve), positive/negative likelihood ratio (PLR/NLR). PLR=sensitivity/(1-specificity); NLR=(1-sensitivity)/specificity. Likelihood ratios were considered as the preferred measure of diagnostic accuracy since they are clinically more meaningful than sensitivities, specificities, or diagnostic odds ratios. They quantify how strongly the likelihood of a disease is changed by the presence (pLR) or absence (nLR) of a symptom or sign. A LR of 1 indicates a test result without any diagnostic value. LRs of 1 to 2 or 0.5 to 1 change the likelihood very little and they are rarely important. LRs ≤0.5 or ≥2 change it at least moderately and can be considered as clinically helpful in the context of medical history taking and physical examination (Furukawa, et al 2008*). Only positive likelihood ratios will be extracted (if present) or calculated because the effectiveness/clinical relevance of identifying at-risk patients with a positive test (pLR) is of higher value than the effectiveness/clinical relevance of identifying at-risk patients with a negative test (nLR). AUC quantifies the overall ability of the test to discriminate between those individuals with the disease and those without the disease. A truly useless test (one no better at identifying true positives than flipping a coin) has an area of 0.5. A perfect test (one that has zero false

	positives and zero false negatives) has an area of 1.00. Classification: AUC 0.90-1 = excellent; 0.80-0.90 = good; 0.70-0.80 = fair; 0.60-0.70 = poor; 0.50-0.60 = fail. We consider a diagnostic test as clinically helpful if AUC>0.7. If only AUC is mentioned, a comparison between two scores should be made and a p-value or narrative description of significance should be mentioned. In case a statistical comparison is made between two triage methods and a p-value is mentioned, a conclusion will be made in favour of a test (if statistically significant). If no p-values are mentioned, and only likelihood ratios are mentioned or calculated, a conclusion will be made on the clinical relevance of the triage method based on the above mentioned cut-off values. **Study design:** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

* Furukawa TA, Strauss S, Bucher HC, Guyatt G. Diagnostic tests. In: Guyatt G, Rennie D, Meade MO, Cook DJ, editors. Users' guides to the medical literature A manual for evidence-based clinical practice. 2nd ed. New York: McGraw Hill Medical; 2008.p. 419-38.

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Abbott, 2015, UK	Diagnostics: diagnostics accuracy study	453 adult patients (mean age 60.9±22.4, 242 female) admitted to the Acute Assessment Unit at a large London teaching hospital between 25th March and 13th April 2013.	NEWS vs PARS	NEWS: National Early Warning Score PARS: Patient at Risk Score
Bulut, 2014, Turkey	Diagnostics: Diagnostic accuracy study	Data of 2000 medical and surgical patients, mean age 61.41±18.92 (1039 males, 961 female) between October 2011 and April 2012 were obtained prospectively.	MEWS vs REMS	MEWS: Modified Early Warning Score REMS: Rapid Emergency Medicine Score Receiver operator characteristics (ROC) curve analysis was performed to evaluate and compare the performances of MEWS and REMS.
Cuthbertson, 2010, Canada	Diagnostics: diagnostic accuracy study	466 patients (65.4±17.4 yrs; 236 males, 230 females) admitted to the acute medical admissions unit or the respiratory unit. For the medical-non ICU and respiratory-non ICU groups, patients were recruited from 21 July until 2	1. EWS 2. MEWS 3. SEWS	EWS: early warning score SEWS: Scottish early warning score

		September 2005. The medical-ICU and respiratory ICU groups were identified retrospectively between January 2005 and December 2005.		

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Mortality & critical care admission	NEWS vs PARS	Statistically significant: OR: 1.54, 95%CI [1.26; 1.91] (p<0.001) vs OR: 1.42, 95%CI [1.00; 2.05] (p=0.056) *In favour of NEWS*	1, 445 (diagnostic accuracy study)	Abbott, 2015
Hospitalization	MEWS vs REMS	AUC MEWS: 0.568, 95%CI [0.546; 0.590] (p<0.001) *The accuracy of MEWS can be considered as 'fail'* AUC REMS: 0.642, 95%CI [0.621; 0.663] (p<0.001) *The accuracy of REMS can be considered as 'poor'* Statistically significant: Difference in performance between MEWS and REMS: (p<0.001)† *In favour of REMS*	1, 2000 (diagnostic accuracy study)	Bulut, 2014
In-hospital mortality		AUC MEWS: 0.630, 95%CI [0.608; 0.651] (p<0.001) *The accuracy of MEWS to identify patients at-risk for in-hospital mortality can be considered as 'poor'.* AUC REMS: 0.707, 95%CI [0.686; 0.727] (p<0.001) *The accuracy of REMS to identify patients at-risk for in-hospital mortality can be considered as 'fair'. REMS can be considered as clinically helpful.* Statistically significant: Difference in performance between MEWS and REMS: (p<0.001)† *In favour of REMS*		
ICU admission		AUC MEWS: 0.538, 95%CI [0.516; 0.560] (p<0.001) *The accuracy of MEWS to identify patients at-risk for ICU admission can be considered as 'fail'.* AUC REMS: 0.589, 95%CI [0.567; 0.611] (p<0.001) *The accuracy of REMS to identify patients at-risk for ICU admission can be considered as 'fail'.* Statistically significant:		

		Difference in performance between MEWS and REMS: (p<0.001)† *In favour of REMS*		
	EWS vs acute medical admission	Sensitivity: 83% Specificity: 70% PLR: 2.77 *† *EWS can be considered as clinically helpful to identify at-risk medical patients*	1, 466 (diagnostic accuracy study)	Cuthbertson, 2010
	MEWS vs acute medical admission	Sensitivity: 83% Specificity: 79% PLR: 3.95 *† *MEWS can be considered as clinically helpful to identify at-risk medical patients*		
	SEWS vs acute medical admission	Sensitivity: 95% Specificity: 77% PLR: 4.13 *† *SEWS can be considered as clinically helpful to identify at-risk medical patients*		
	EWS vs acute respiratory admission	Sensitivity: 66% Specificity: 59% PLR: 1.61 *†		
	MEWS vs acute respiratory admission	Sensitivity: 77% Specificity: 68% PLR: 2.41 *† *MEWS can be considered as clinically helpful to identify at-risk respiratory patients*		
	SEWS vs acute respiratory admission	Sensitivity: 84% Specificity: 70% PLR: 2.80 *† *SEWS can be considered as clinically helpful to identify at-risk respiratory patients*		

* Calculations done by the reviewer

£ No CI available

† Imprecision (lack of data)

Quality of evidence

Author, Year	Could the selection of patients have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?	Could the reference standard, its conduct, or its interpretation have introduced bias?	Could the patient flow have introduced bias?	Other limitations
Abbott, 2015	No	Yes, parameters recorded on admission were used in calculating NEWS and PARS	Unclear	No	
Bulut, 2014	Yes, patients with trauma were not included	Yes, parameters recorded on admission were used in calculating MEWS and REMS	Unclear	No	

Cuthbertson, 2010	No	Yes, parameters recorded on admission were used in calculating EWS scores	Unclear	No	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	lack of data
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading low [C]**	

Conclusion	Statistical significance between EWS and other methods: There is limited evidence in favour of using the Early Warning Score (and its modified forms such as MEWS, SEWS and NEWS) for the identification of at-risk patients. It was shown that NEWS/MEWS resulted in a statistically significant increased identification of patients at risk for mortality and critical care admission, compared to PARS (Abbott 2015, Bulut 2014). However, it was shown that MEWS resulted in a statistically significant decreased identification of patients at risk of hospitalization, in-hospital mortality and ICU admission, compared to REMS (Bulut 2014). Clinical helpfulness of EWS: The accuracy of MEWS to identify patients at risk of hospitalisation, in-hospital mortality and ICU admission can be considered as 'fail' to 'poor' (Bulut 2014). Furthermore, MEWS and SEWS can be considered as clinically helpful for the identification of patients at risk of acute medical or respiratory admission. Also, EWS can be considered as clinically helpful for the identification of patients at risk of acute medical admission. However, EWS cannot be considered clinically helpful for the identification of patients at-risk for respiratory admission. (Cuthbertson 2010) Evidence is of low quality and results of these studies are imprecise due to lack of data.
Reference(s)	**Articles** Abbott TEF, Vaid N, Ip D, Cron N, Wells M. *A single-centre observational cohort study of admission National Early Warning Score (NEWS)*. Resuscitation 2015, 92:89-93 Bulut M, Cebicci H, Sigirli D, Sak A, Durmus O, Top AA, Kaya S, Uz K. *The comparison of modified early warning score with rapid emergency medicine score: a prospective multicenter observational cohort study on medical and surgical patients presenting to emergency department*. Emerg Med J 2014, 31:476-481 Cuthbertson BH, Boroujerdi M, Prescott G. *The use of combined physiological parameters in the early recognition of the deteriorating acute medical patient.* J R Coll Physicians Edinb 2010, 40:19-25

Triage – MIST method

Question (PICO)	When transferring a victim from one first responder to another (P), does transfer of information according to the MIST-method (Mechanism of injury, Injuries found and suspected, Signs, Treatment given) (I) compared to no or another method of information transfer (C), proceed more correct (O)?
Search Strategy	Databases

	The Cochrane Library (systematic reviews and controlled trials) using the following search strategy: 1. MIST:ti,ab,kw OR (mechanism:ti,ab,kw AND injur*:ti,ab,kw AND (sign:ti,ab,kw OR signs:ti,ab,kw) AND treatment*:ti,ab,kw) 2. [mh "patient transfer"] OR transfer*:ti,ab,kw OR handover:ti,ab,kw OR [mh triage] OR triage:ti,ab,kw OR [mh checklist] 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. MIST[TIAB] OR (mechanism*[TIAB] AND injur*[TIAB] AND (sign[TIAB] OR signs[TIAB]) AND treatment*[TIAB]) 2. "Patient transfer"[Mesh] OR transfer*[TIAB] OR handover[TIAB] OR triage[Mesh] OR triage[TIAB] OR checklist[Mesh] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. MIST:ab,ti OR (mechanism*:ab,ti AND injur*:ab,ti AND (sign:ab,ti OR signs:ab,ti) AND treatment*:ti,ab) 2. 'patient transport'/exp OR transfer*:ab,ti OR handover:ab,ti OR 'emergency health service'/exp OR triage:ab,ti OR checklist/exp 3. 1-2 AND
Search date	16 July 2015
In/Exclusion criteria	**Population**: paramedics, medical and nursing clinicians **Intervention**: MIST-method for paramedic-to-emergency department staff handovers **Comparison**: other methods of handovers **Outcome**: times questions are asked during handovers, questioning already given information, times paramedic will repeat info post-question **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Blood pressure measurement – Automatic vs manual (Diagnostics)

Question (PICO)	In humans (P), should automatic blood pressure measurement (I) versus manual blood pressure management (C) be used to measure blood pressure (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "blood pressure determination"] OR [mh sphygmomanometers] OR "blood pressure":ti,ab,kw OR sphygmo*:ti,ab,kw 2. [mh "blood pressure monitoring, ambulatory"] OR Electronic:ti,ab,kw OR automat*:ti,ab,kw OR digital:ti,ab,kw OR "home blood pressure":ti,ab,kw 3. Conventional:ti,ab,kw OR manual:ti,ab,kw 4. 1-3 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "blood pressure determination"[Mesh] OR "blood pressure*"[TIAB] OR sphygmomanometers[Mesh] OR sphygmo*[TIAB] 2. "Blood Pressure Monitoring, Ambulatory"[Mesh] OR electronic*[TIAB] OR automat*[TIAB] OR digital[TIAB] OR "home blood pressure"[TIAB] 3. Conventional[TIAB] OR manual[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'Blood pressure monitoring'/exp OR 'blood pressure monitor'/exp OR 'blood pressure meter'/exp OR 'sphygmomanometer'/exp OR 'blood pressure measurement'/exp OR 'blood pressure':ab,ti OR sphygmo*:ab,ti 2. Ambulatory:ab,ti OR Electronic:ab,ti OR automat*:ab,ti OR digital:ab,ti OR 'home blood pressure':ab,ti 3. Conventional:ab,ti OR manual:ab,ti 4. 1-3 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	09-07-2015
In/Exclusion criteria	**Population**: Include: Healthy individuals or people with hypotension or hypertension. Exclude: pregnant women, people with medical conditions such as diabetes,… **Intervention**: Include: Measurement of blood pressure with automated blood pressure measurement and manual blood pressure management. Exclude: Automated office blood pressure measurement (taking more than 1 measurement at once). **Comparison** Include: Gold standard: mean awake 24-hour ambulatory blood pressure monitoring. Exclude: studies that make the direct comparison between automated and manual BP measurement. **Outcome**: Include: Systolic and diastolic blood pressure. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available.

	Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Stergiou, 1997, Greece	Experimental: randomised controlled trial (within subjects design)	46 patients with essential hypertension who attended the Outpatients Blood Pressure Clinic for at least 2 months, who were untreated or were on stable antihypertensive treatment for at least 4 weeks, and who measured HPB with aneroid sphygmomanometers for at least 6 months before study entry. Patients were randomly allocated to the sHBP group or to the oHBP group for two weeks. After that, patients switched groups for another 2 weeks.	1. oHBP vs ABP 2. sHBP vs ABP 3. oHBP vs sHBP	Patients received a 30 min training on BP measurements. • oHBP: oscillometric home blood pressure measurement (=automated) • sHBP: stethoscopic home BP measurement (with aneroid sphygmomanometer) • ABP: ambulatory blood pressure (portable oscillometric devices SpaceLabs 90207, applied on a workday between first and second HBP measurement period. BP was measured at 20 min intervals for 24h)

Synthesis of findings

Outcome	Comparison/Risk factor	Effect Size	#studies, # participants	Reference
systolic BP	ABP vs sHBP	Not statistically significant: MD: -1.4, 95%CI [-25.8; 23.0] (p=0.45) £†	1, 46 vs 46 § (within subjects)	Stergiou, 1997
	ABP vs oHBP	Not statistically significant: MD: -0.6, 95%CI [-25.0; 23.8] (p=0.74) £†		
	sHBP vs oHBP	Not statistically significant: MD: 0.7, 95%CI [-15.9; 17.3] (p=0.59) £†		
Diastolic BP	ABP vs sHBP	Not statistically significant: MD: 0.9, 95%CI [-15.9; 17.7] (p=0.45) £†		
	ABP vs oHBP	Not statistically significant: MD: 1.9, 95%CI [-12.7; 16.5] (p=0.08) £†		
	sHBP vs oHBP	Not statistically significant: MD: 1.1, 95%CI [-12.1; 14.3] (p=0.28) £†		

£ No raw data/SD's available

† Imprecision (lack of data)

§ Imprecision (limited sample size)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Stergiou, 1997	Unclear, patients were randomly allocated, but not mentioned how	Yes, but not possible	No	No	within subjects design

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/lack of data
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is limited evidence neither in favour of the intervention nor the control. A statistically significant difference in systolic or diastolic blood pressure, using automated compared to manual blood pressure measurement, could not be demonstrated (Stergiou 1997). Evidence is of low quality and results of this study are imprecise due to limited sample size.
Reference(s)	**Articles** Stergiou GS, Voutsa AV, Achimastos AD, Mountokalakis TD. *Home self-monitoring of blood pressure. Is fully automated oscillometric technique as good as conventional stethoscopic technique?* Am J Hypertens 1997, 10:428-433

Blood pressure measurement – Laypeople vs professionals

Question (PICO)	In humans (P), does having blood pressure measured by laypeople (I) compared to having it measured by a professional first responder (C) give less correct results (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "blood pressure determination"] OR [mh sphygmomanometers] OR "blood pressure":ti,ab,kw OR sphygmo*:ti,ab,kw 2. [mh "blood pressure monitoring, ambulatory"] OR Electronic:ti,ab,kw OR automat*:ti,ab,kw OR digital:ti,ab,kw OR "home blood pressure":ti,ab,kw 3. Conventional:ti,ab,kw OR manual:ti,ab,kw 4. 1-3 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "blood pressure determination"[Mesh] OR "blood pressure*"[TIAB] OR sphygmomanometers[Mesh] OR sphygmo*[TIAB] 2. "Blood Pressure Monitoring, Ambulatory"[Mesh] OR electronic*[TIAB] OR automat*[TIAB] OR digital[TIAB] OR "home blood pressure" 3. Conventional[TIAB] OR manual[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy:

	1. 'Blood pressure monitoring'/exp OR 'blood pressure monitor'/exp OR 'blood pressure meter'/exp OR 'sphygmomanometer'/exp OR 'blood pressure measurement'/exp OR 'blood pressure':ab,ti OR sphygmo*:ab,ti 2. Ambulatory:ab,ti OR Electronic:ab,ti OR automat*:ab,ti OR digital:ab,ti OR 'home blood pressure':ab,ti 3. Conventional:ab,ti OR manual:ab,ti 4. 1-3 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	09-07-2015
In/Exclusion criteria	**Population**: Include: Laypeople, people without experience in blood pressure measurement. **Intervention**: Include: Measurement of blood pressure by laypeople **Comparison** Include: Measurement of blood pressure by experienced people, i.e. doctors, nurses,… **Outcome**: Include: Correct blood pressure measurement. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria
Reference(s)	/

Neurologic stability – Pupils check

Question (PICO)	In humans with a possible traumatic brain injury (P), are anisocoria, mydriasis or miosis (RF) compared to normal pupils (C) a risk factor for unfavourable neurological outcome or mortality (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh anisocoria] OR anisocoria:ti,ab,kw OR [mh mydriasis] OR mydriasis:ti,ab,kw OR [mh miosis] OR miosis:ti,ab,kw OR isocoria:ti,ab,kw

	2. [mh "brain injuries"] OR ((brain:ti,ab,kw OR head:ti,ab,kw) AND injur*:ti,ab,kw) OR "neurologic *stability":ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. anisocoria[Mesh] OR anisocoria[TIAB] OR mydriasis[Mesh] OR mydriasis[TIAB] OR miosis[Mesh] OR miosis[TIAB] OR isocoria[TIAB] 2. "brain injuries"[Mesh] OR ((brain[TIAB] OR head[TIAB]) AND injur*[TIAB]) OR "neurologic *stability"[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Anisocoria/exp OR anisocoria:ab,ti OR mydriasis/exp OR mydriasis:ab,ti OR miosis/exp OR miosis:ab,ti OR isocoria:ab,ti 2. 'brain injury'/exp OR ((brain:ab,ti OR head:ab,ti) AND injur*:ab,ti) OR (neurologic NEXT (stability OR instability)):ab,ti 3. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	26 August 2015
In/Exclusion criteria	**Population**: Include: People with possible traumatic brain injury due to road accident, automobile accident, fall, motorcycle accident, aggression, bicycle accident or others. Exclude: victims of gunshot injury and patients who evolved to brain death before 24 hours of admission. **Intervention**: Pupils examination **Outcome**: Mortality, unfavourable neurologic outcome, brain injury **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies. **Language**: Include: English **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Risk factor	Remarks
Martins, 2009, Brasil	Observational: cohort study	748 consecutive patients (631 male; mean age 34.8±16.3 years) with severe traumatic brain injury (TBI) admitted to the intensive care unit of the Hospital Governador Celso Ramos between January 1, 1994 and December 31, 2004.	1. Miotics 2. Anisocorics 3. Mydriatics 4. Isocorics	Miosis: constriction of pupil Anisocoria: unequal size of pupils Mydriasis: dilation of the pupil Isocoria: equal sized pupils
Park, 2009, Korea	Observational: cohort study	115 patients (81 male, 34 female; mean age 47.7 years (range 16.8-85.2)) who were admitted to the neurosurgical department via the emergency room due to head trauma.	At least unilateral dilated pupils vs absent pupil dilation	Neurological outcome was evaluated with the Glasgow Outcome Scale (GOS), the Disability rating scale (DRS) and the

				Rancho Los Amigos Cognitive Scale (LCFS)
Wolf, 2014, Austria	Observational: cohort study	12786 trauma patients (mean age 37.5±28.4 years) admitted to a university-based Level-I trauma center within a period of 16 months between January 2005 and April 2006.	anisocoria vs isocoria	

Synthesis of findings

Outcome	Risk factor	Effect Size	#studies, # participants	Reference
Mortality	Miotics vs Isocorics	Not statistically significant: 7/30 vs 44/283 § aOR: 1.47, 95%CI [0.53; 4.07] ¥ (p=0.40)	1, 30 vs 283	Martins, 2009
	Anisocorics vs Isocorics	Statistically significant: 131/347 vs 44/283 § aOR: 2.65, 95%CI [1.69; 4.17] (p<0.0001) *With harm for anisocorics*	1, 347 vs 283	
	Mydriatics vs Isocorics	Statistically significant: 66/83 vs 44/283 § aOR: 11.24, 95%CI [5.42; 23.30] (p<0.0001) *With harm for mydriatics*	1, 83 vs 283	
Unfavourable neurologic outcome (according to GOS)	At least unilateral dilated pupils vs absent pupil dilation	Statistically significant: 14/27 vs 14/88 § OR: 5.69, 95%CI [2.21; 14.67] (p=0.0003) * *With harm for at least unilateral dilated pupils*	1, 27 vs 88	Park, 2009
Unfavourable neurologic outcome (according to DRS)		Statistically significant: 15/27 vs 16/88 § OR: 5.63, 95%CI [2.22; 14.29] (p=0.0003) * *With harm for at least unilateral dilated pupils*		
Unfavourable neurologic outcome (according to LCFS)		Statistically significant: 17/27 vs 20/88 § OR: 5.78, 95%CI [2.29; 14.60] (p=0.0002) * *With harm for at least unilateral dilated pupils*		
Brain injury	anisocoria vs isocoria	Statistically significant: aOR: 4.39, 95%CI [2.716; 7.097] † (p<0.0001) *With harm for anisocoria*	1, 489 § (not mentioned how many in each group)	Wolf, 2014

Mean ± SD (unless otherwise indicated)

* Calculations done by the reviewer(s) using Review Manager software

¥ Imprecision (large variability of results)

† Imprecision (lack of data)

§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations
Martins, 2009	No	No	No	No	
Park, 2009	No	No	No	No	
Wolf, 2014	Unclear	No	No	No	

Level of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Low number of events/lack of data/large variability of the results
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Very Low [D]**	

Conclusion	There is limited evidence with harm for anisocoria, miosis, mydriasis. It was shown that anisocoris, mydriasis and miosis resulted in a statistically significant increased risk of mortality, unfavourable neurological outcomes or brain injury, compared to isocoria (Martins 2009, Park 2009, Wolf 2014). Evidence is of very low quality and results cannot be considered precise due to limited sample size, lack of data and/or large variability of results.
Reference(s)	**Individual studies** Martins ET, Linhares MN, Sousa DS, Schroeder HK, Meinerz J, Rigo LA, Bertotti MM, Gullo J, Hohl A, Dal-Pizzol F, Walz R. *Mortality in severe traumatic brain injury: a multivariated analysis of 748 Brazilian patients from Florianópolis City*. J Trauma 2009, 67:85-90 Park J-E, Kim S-H, Yoon S-H, Cho KG, Kim S-H. *Risk factors predicting unfavorable neurological outcome during the early period after traumatic brain injury*. J Korean Neurosurg Soc 2009, 45:90-95

Medical assessment – SAMPLE history

Question (PICO)	In humans (P), should SAMPLE (I) be used to obtain a patient's medical assessment (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. "Sample history":ti,ab,kw 2. Symptom*:ti,ab,kw AND allerg*:ti,ab,kw AND medication*:ti,ab,kw AND "oral intake":ti,ab,kw 3. 1-2 OR **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Sample history"[TIAB] 2. Symptom*[TIAB] AND Allerg*[TIAB] AND Medication*[TIAB] AND "oral intake"[TIAB] 3. 1-2 OR **Embase** (via Embase.com interface) using the following search strategy: 1. 'SAMPLE history':ab,ti 2. Symptom*:ab,ti AND allerg*:ab,ti AND medication:ab,ti AND 'oral intake':ab,ti 3. 1-2 OR
Search date	26 August 2015
In/Exclusion criteria	**Population**: Patients with an injury or illness

	Intervention: information collection with SAMPLE (Symptoms, Allergies, Medications, Past medical history, Last oral intake, Events leading up to present illness/injury) **Outcome**: Medical history **Study design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study (accuracy study): inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Immobilization and transport – vacuum mattress vs backboard

Question (PICO)	In patients requiring spinal immobilization (P) is a vacuum mattress (I) better than a long spinal board (C) at providing comfort and immobilization (O)?
Search Strategy	Databases **GIN, NGC** (guidelines) using the search terms 'spine injury' OR 'cervical injury' OR 'backboard' OR 'spine board' OR 'vacuum mattress' **BestBET** (best evidence topics) using the search terms: 'spine' OR 'cervical' OR 'board' **The Cochrane Library** (systematic reviews) using the following search term: MeSH descriptor: [spinal injury] explode all trees **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Spinal injury"] OR ((cercival:ti,ab,kw OR spinal:ti,ab,kw) AND injur*:ti,ab,kw) 2. "backboard":ti,ab,kw OR "mattress":ti,ab,kw OR 'spine board':ti,ab,kw OR "vacuum":ti,ab,kw OR "log roll":ti,ab,kw OR [mh "Patient Transfer"] 3. #1 and #2 **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Cervical Vertebrae/injuries"[Mesh] OR "Spinal Cord Injuries"[Mesh] OR ((cervical[TIAB] OR spinal[TIAB]) AND injur*[TIAB])

	2. backboard [TIAB] OR "spine board" [TIAB] OR vacuum [TIAB] OR padded [TIAB] OR mattress [TIAB] OR "Immobilization" [Mesh] OR "Transportation of Patients"[Mesh] OR "log roll"[TIAB] OR "patient transport"[TIAB] OR "6-plus-person"[TIAB] OR 6PP[TIAB] 3. 1 AND 2 **Embase** (via Embase.com interface) using the following search strategy: 1. 'spinal cord injury'/exp OR 'cervical spine'/exp OR ((cervical:ab,ti OR spinal:ab,ti) AND injur*:ab,ti) 2. 'fracture immobilization'/exp OR 'backboard':ab,ti OR 'spine board':ab,ti OR 'vacuum':ab,ti OR 'mattress':ab,ti OR 'stretcher':ab,ti OR 'padded':ab,ti OR 'splint':ab,ti OR ('patient transport'/exp OR 'patient transport':ab,ti OR 'log roll':ab,ti OR '6-plus-person':ab,ti) 3. 1 AND 2 Systematic reviews used as source for individual studies: Ahmad 2007, BestBET 'Spinal boards or vacuum mattresses for immobilisation'. Ahn H 2011, Pre-hospital care management of a potential spinal cord injured patient: a systematic review of the literature and evidence-based guidelines Kwan I 2009, Cochrane review: Spinal immobilization for trauma patients. Selected articles were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	02 July 2015
In/Exclusion criteria	**Population**: We included studies with healthy volunteers or trauma victims. **Intervention**: Include: vacuum mattress Exclude: devices which are only used in emergency departments (such as special types of mattresses). **Comparison**: Include: long spinal board, unpadded backboard **Outcome**: We included studies measuring comfort and pain or immobilization. We excluded studies measuring biomechanical markers (respiratory volumes) **Study design** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year:** Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Chan, 1996, USA	Experimental: Randomized controlled trial (within subjects design)	27 healthy volunteers, aged 17-49 years, without history of back pain/spinal disease	Immobilisation (30min) on: • Wooden backboard • Mattress-splint Both groups also had a StifNeck collar	
Cross, 2001, USA	Experimental: Randomized controlled trial	18 healthy volunteers (10 female, 8 male), mean age 34 (range 18-54 years), without	Immobilisation (60min) on: • Hard spine board • Vacuum splint (model 1) • Vacuum splint (model 2)	sample size was based on results of an earlier study

	(within subjects design)	history of back pain/spinal disease		
Hamilton, 1996, USA	Experimental: Randomized controlled trial (within subjects design)	26 healthy volunteers (22 men, 4 women), mean age 28.9±9 years, without history of back/neck pain	Immobilisation on: • Spine board (with/without StifNeck collar) • Mattress-splint (with/without StifNeck collar)	
Johnson, 1996, USA	Experimental: Randomized controlled trial (within subjects design)	30 healthy students (to test comfort) + 30 extra students (to test immobilization)	Immobilisation (30min) on: • Wooden backboard (with/without StifNeck collar) • Mattress-splint (with/without StifNeck collar)	
Keller, 2005, The Netherlands	Experimental: Randomized controlled trial (within subjects design)	20 healthy volunteers, average age 40 years (range 20-56 years) without history of back pain	Immobilisation on: • Spinal board • Vacuum mattress • ER-overlay mattress [data on ER-overlay mattress were not extracted]	
Lovell, 1994, UK	Experimental: Non-randomized controlled trial (within subjects design)	30 healthy volunteers	Immobilisation on: • Spinal board • Padded spinal board • Vacuum stretcher	
Luscombe, 2003, UK	Experimental: Non-randomized controlled trial (within subjects design)	9 healthy volunteers (8 male, 1 female)	Immobilisation on: • Backboard • Vacuum mattress	
Mahshidfar, 2013, Iran	Experimental: randomized controlled trial	60 trauma victims (49 male, 11 female) with possible spinal trauma were randomly assigned to either LBB (n=30), mean age 30.25±2.95 years or VMS (n=30); mean age 35.50±3.13 years	Immobilisation on: • Long backboard (LBB): Spencer Rock plastic backboard stretcher with Spencer contour head immobilizer • Vacuum mattress splint (VMM): Attucho "NYB" vacuum mattress TPU In both cases, the cervical spine was immobilized immediately using a rigid cervical collar.	
Sheerin, 2007, Ireland	Experimental: Non-randomized controlled trial (within subject design)	2 healthy male volunteers, 41 and 23 years old	Interface pressure (sacral and occipital) on: • Spinal board • Padded spinal board • Vacuum stretcher	
Totten, 1999, USA	Experimental: Randomized controlled trial (within subjects design)	39 healthy volunteers (20 male, 19 female), mean age 40.43±26.65 years,	Immobilisation on: • Wooden backboard • Vacuum mattress Both groups were wearing a collar.	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Number of persons with pain symptoms	wooden backboard vs vacuum mattress splint	Statistically significant: 28/37 vs 9/28 Adjusted RR: 3.08, 95%CI [1.74;5.44], p<0.0001 *In favour of vacuum mattress*	1, 37 vs 28 § (within subjects design)	Chan 1996
	hard spine board vs vacuum splint (model 1) vs vacuum splint (model 2)	After 30 min: Statistically significant: Occiput: 14/18 vs 5/18 vs 6/18 £†§ p<0.01 *In favour of vacuum splints* Lower back: 10/18 vs 1/18 vs 3/18 £†§ p<0.01 *In favour of vacuum splints* Not statistically significant: Neck: 6/18 vs 4/18 vs 1/18 £†§ p=0.15 Upper back 6/18 vs 3/18 vs 3/18 £†§ p=0.41 Sacrum: 10/18 vs 7/18 vs 5/18 £†§ p=0.21 Elbows: 0/18 vs 0/18 vs 1/18 £†§ p=0.37 Heels/ankles 4/18 vs 1/18 vs 2/18 £†§ p=0.25 After 60 min: Statistically significant: Occiput: 15/18 vs 6/18 vs 6/18 £†§ p<0.01 *In favour of vacuum splints* Lower back: 7/18 vs 2/18 vs 4/18 £†§ p=0.04 *In favour of vacuum splints* Not statistically significant: Neck: 6/18 vs 4/18 vs 4/18 £†§ p=0.61	1, 18 vs 18 vs 18 (within subjects design)	Cross 2001

		Upper back: 7/18 vs 5/18 vs 7/18 £†§ p=0.72 Sacrum: 10/18 vs 7/18 vs 5/18 £†§ p=0.15 Elbows: 0/18 vs 0/18 vs 2/18 £†§ p=0.14 Heels/ankles 4/18 vs 1/18 vs 2/18 £†§ p=0.25		
Pain (10-point scale; 0=more pain)	backboard vs vacuum splint	<u>Statistically significant:</u> Median: 6 vs 3 p<0.001 £† *In favour of vacuum splint*	1, 30 vs 30 § (within subjects design)	Johnson 1996
Discomfort (10-point scale; 0=no discomfort)	backboard vs backboard with Stifneck collar vs vacuum splint vs vacuum splint with Stifneck collar	<u>Statistically significant:</u> 3.4±1.3 vs 3.2±1.4 vs 1.0±0.7 vs 1.2±1.0 £† p<0.05 *In favour of vacuum splint (with and without Stifneck collar)*	1, 26 vs 26 vs 26 vs 26 § (within subjects design)	Hamilton 1996
Comfort (1-10 scale; 1=no pain)	backboard vs vacuum mattress	<u>Statistically significant:</u> 4.6±1.2 vs 6.6±1.3 MD:-2.00 £†, p<0.05 *In favour of vacuum mattress*	1, 20 vs 20 § (within subjects design)	Keller 2005
	backboard vs vacuum mattress	<u>Statistically significant:</u> 5.22 vs 1.88 MD: 3.34, 95%CI [2.12;4.55] p<0.01 *In favour of vacuum mattress*	1, 9 vs 9 § (within subjects design)	Luscombe 2003
High patient comfort	long backboard vs vacuum mattress splint	<u>Statistically significant:</u> 16/30 vs 0/30 £†§ p<0.001 *In favour of long backboard*	1, 30 vs 30	Mahshidfar 2013
Comfort (1-6 scale; 1=very uncomfortable)	wooden backboard vs vacuum mattress	<u>Statistically significant:</u> 2.8±1.25 vs 4.8±0.92 MD: -2.00 £†, p<0.001 *In favour of vacuum mattress*	1, 39 vs 39 § (within subjects design)	Totten 1999
Sacral interface pressure (mmHg)	backboard- padded backboard vs vacuum mattress	<u>Statistically significant:</u> 147.3 vs 115.5 vs 36.7 p<0.05 £† *In favour of vacuum matress*	1, 30 vs 30 § (within subjects design)	Lovell 1994
	backboard vs vacuum mattress	Not statistically significant: 174.9±15.8 vs 165.6±29.0 MD: 9.30 £†, p>0.05	1, 20 vs 20 § (within subjects design)	Keller 2005
	backboard vs vacuum mattress	<u>Statistically significant:</u> 136.33±25.45 - 65.5±7.31 MD:70.83, 95%CI [34.12 ;107.54], p=0.0002 *In favour of vacuum mattress*	1, 2 vs 2 § (within subjects design)	Sheerin 2007

	padded backboard vs vacuum mattress	Not statistically significant: 59.5±23.33 vs 65.5±7.31 MD: -6.00, 95%CI [-39.88;27.88], p=0.73 ¥		
Scapulae interface pressure (mmHg)	backboard vs vacuum mattress	Statistically significant 176.6±3.6 vs 131.6±50.9 MD: 45.0 £†, p<0.05 *In favour of the vacuum mattress*	1, 20 vs 20 § (within subjects design)	Keller 2005
Heels interface pressure (mmHg)	backboard vs vacuum mattress	Statistically significant: 153.0±16.1 vs 123.3±45.2 MD:29.70 £†, p<0.05 *In favour of the vacuum mattress*		
Occipital interface pressure (mmHg)	backboard vs vacuum mattress	Statistically significant: 87.25±10.96 vs 59.5±7.77 MD: 28.05, 95%CI [9.42;46.68], p=0.003 *In favour of vacuum mattress*	1, 2 vs 2 § (within subjects design)	Sheerin 2007
	padded backboard vs vacuum mattress	Not statistically significant: 61.67±7.07 vs 59.5±7.77 MD: 2.47, 95%CI [-12.10;17.04], p=0.74		
Immobilization (overall) (10-point scale; 0=more mobile)	backboard vs backboard with Stifneck collar vs vacuum splint vs vacuum splint with Stifneck collar	Statistically significant: 6.6±1.5 vs 7.5±1.0 vs 7.3±1.0 vs 8.1±1.0 £† p>0.05 *In favour of vacuum splint with Stifneck collar*	1, 26 vs 26 vs 26 vs 26 § (within subjects design)	Hamilton 1996
Head movement (cm)	Backboard vs vacuum splint	Statistically significant: 2.6±1.1 vs 4.3±1.6 MD:-1.70, p<0.001 *In favour of vacuum splint*	1, 60 vs 60 § (within subjects design)	Johnson 1996
	Backboard with Stifneck collar vs vacuum splint with Stifneck collar	Statistically significant: 2.8±1.1 vs 4.0±1.4 MD:-1.20 £†, p<0.001 *In favour of vacuum splint*		
	backboard vs vacuum mattress	Statistically significant: Head up: 2.330 vs 0.666 MD: 1.664, 95%CI [0.961;3.878] p<0.01 *In favour of vacuum mattress* Head down: 4.089 vs 0.833 MD: 3.256, 95%CI [1.590;6.920] p<0.01 *In favour of vacuum mattress* Lateral tilt: 1.833 vs 0.426 MD:1.407, 95%CI [0.666 to 2.942], p<0.01 *In favour of vacuum mattress*	1, 9 vs 9 § (within subjects design)	Luscombe 2003

Shoulder movement (cm)	Backboard vs vacuum splint	Not statistically significant: 4.1±1.7 vs 3.5±1.6 MD: 0.60 £†, p>0.05	1, 60 vs 60 § (within subjects design)	Johnson 1996
	Backboard with Stifneck collar vs vacuum splint with Stifneck collar	Statistically significant: 4.6±1.6 vs 3.4±1.7 MD:1.20 £†, p<0.003 *In favour of backboard*		
Hip movement (cm)	Backboard vs vacuum splint	Statistically significant: 3.4±1.5 vs 1.3±0.9 MD: 2.10 £†, p<0.001 *In favour of backboard*		
	Backboard with Stifneck collar vs vacuum splint with Stifneck collar	Statistically significant: 3.4±1.6 vs 1.4±1.0 MD: 2.0 £†, p<0.001 *In favour of backboard*		
High Immobilisation	long backboard vs vacuum mattress splint	Statistically significant: Flexion & extension: 17/30 vs 0/30 £†§ p<0.001 *In favour of long backboard* Lateral bending 13/30 vs 0/30 £†§ p<0.001 *In favour of long backboard* Rotation 25/30 vs 0/30 £†§ p<0.001 *In favour of long backboard* Thoraco-lumbar 12/30 vs 0/30 £†§ p<0.001 *In favour of long backboard*	1, 30 vs 30	Mahshidfar 2013

Mean ± SD (unless otherwise indicated)
£ No SD's available, effect size and CI cannot be calculated
¥ Imprecision (large variability of results)
† Imprecision (lack of data)
§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations	Remarks
Chan, 1996	Unclear, not specified in the article	Yes	No	No	Cross-over study	
Cross, 2001	Unclear, not specified in the article	Yes, participants are doing both interventions and make a self-evaluation	No	No	Cross-over study	

Hamilton, 1996	Unclear, not specified in the article	Yes, participants are doing both interventions and make a self-evaluation	No	No	Cross-over study	
Johnson, 1996	Unclear, not specified in the article	Yes	No	No	Cross-over study; way of randomization unclear	
Lovell, 1994	Yes	Yes	No	No	No randomization, within subjects	As the thoracic sensor is not touching the surface on the backboard, no interface pressure can be measured
Luscombe 2003	Yes	Yes	No	No	No randomization, within subjects	
Mahshidfar, 2013	No	Yes, but irrelevant	no	no		
Sheerin 2007	Yes	Yes	No	No	No randomization, within subjects, very small population	
Totten 1999	Unclear, not specified in the article	Yes	No	No	Cross-over study; way of randomization unclear	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes
Inconsistency	0	
Indirectness	-1	Most studies with healthy individuals
Publication bias	0	
QUALITY (GRADE)	**Final grading Very Low [D]**	

Conclusion	**Pain - comfort:** There is conflicting evidence from 8 experimental studies. It was shown that the long backboard resulted in a statistically significant increase of comfort in trauma patients with possible spinal injury, compared to the vacuum mattress splint (Mahshidfar 2013). However, in studies with healthy volunteers, it was shown that the long backboard resulted in a statistically significant increase of pain/discomfort, compared to the vacuum matress (Chan 1996, Cross 2001, Johnson 1996, Hamilton 1996, Keller 2005, Luscombe 2003, Totten 1999). Evidence is of very low quality and results cannot be considered precise due to limited sample size. **Interface pressure:**

	There is limited evidence from 3 experimental studies in favour of the vacuum mattress. In making this evidence conclusion, we place a higher value on statistical outcomes over non-statistical outcomes. It was shown that the vacuum mattress resulted in a statistically significant decrease of sacral, scapulae, heels, occipital interface pressure, compared to the backboard (Lovell 1994, Keller 2005, Sheerin 2007). A statistically significant decrease of sacral interface pressure, using the vacuum mattress compared to the backboard or padded backboard, could not be demonstrated (Keller 2005, Sheerin 2007). Evidence is of very low quality and results cannot be considered precise due to limited sample size, lack of data and/or large variability of results. **Immobilisation:** There is conflicting evidence from 4 experimental studies It was shown that the vacuum mattress resulted in a statistically significant increase of immobilisation in healthy volunteers, compared to the long spinal board (Johnson 1996, Hamilton 1996, Luscombe 2003). However, in studies with trauma patients with possible spinal injury, it was shown that the vacuum mattress resulted in a statistically significant decrease of immobilisation, compared to the long spinal board (Mahshidfar 2013). Evidence is of very low quality and results cannot be considered precise due to limited sample size.
Reference(s)	**Articles** Chan D, Goldberg RM, Mason J, Chan L. *Backboard versus mattress splint immobilization: a comparison of symptoms generated*. J Emerg Med. 1996, 14(3):293-298 Cross DA, Baskerville J. *Comparison of perceived pain with different immobilization techniques.* Prehosp Emerg Care. 2001, 5(3):270-274 Hamilton RS and Pons PT. *The efficacy and comfort of full-body vacuum splints for cervical-spine immobilization*. J Emerg Med 1996, 14(5):553-559 Johnson DR, Hauswald M, Stockhoff C. *Comparison of a vacuum splint device to a rigid backboard for spinal immobilization.* Am J Emerg Med. 1996, 14(4):369-372 Keller BP, Lubbert PH, Keller E, Leenen LP. *Tissue-interface pressures on three different support-surfaces for trauma patients.* Injury. 2005, 36(8):946-948 Lovell ME, Evans JH. *A comparison of the spinal board and the vacuum stretcher, spinal stability and interface pressure*. Injury. 1994, 25(3):179-180 Luscombe MD, Williams JL. *Comparison of a long spinal board and vacuum mattress for spinal immobilisation*. Emerg Med J. 2003, 20(5):476-478 Main PW, Lovell ME. *A review of seven support surfaces with emphasis on their protection of the spinally injured*. J Accid Emerg Med. 1996, 13(1):34-37 Mahshidfar B, Mofidi M, Yari A, Mehrsorosh S. *Long backboard versus vacuum mattress splint to immobilize whole spine in trauma victims in the field: a randomized clinical trial*. Prehospital and Disaster Medicine 2013, 28(5):462-465 Sheerin F, de Frein R. *The occipital and sacral pressures experienced by healthy volunteers under spinal immobilization: a trial of three surfaces*. J Emerg Nurs. 2007, 33(5):447-450 Totten V, Sugarman D. *Respiratory effects of spinal immobilization*. Prehosp Emerg Care. 1999, 3(4):347-352 **Systematic reviews** Ahmad M, Butler J. *BestBET: Spinal boards or vacuum mattresses for immobilisation.* BestBET 2007 Ahn H, Singh J, Nathens A, MacDonald RD, Travers A, Tallon J, Fehlings MG, Yee A. *Pre-hospital care management of a potential spinal cord injured patient: a systematic review of the literature and evidence-based guidelines.* J Neurotrauma. 2011, 28(8):1341-1361. Kwan I, Bunn F, Roberts IG. *Spinal immobilization for trauma patients*. Cochrane review 2009

Spine injury – Vacuum mattress (Feasibility)

Question (PICO)	In humans with a spinal injury (P), is application of a vacuum mattress by laypeople (I) compared to application of a vacuum mattress by professional first responders (C) less effective to change survival, functional recovery, pain, complications, time to resolution of symptoms (O)?
Search Strategy	Databases **GIN, NGC** (guidelines) using the search terms 'spine injury' OR 'cervical injury' OR 'backboard' OR 'spine board' OR 'vacuum mattress' **BestBET** (best evidence topics) using the search terms: 'spine' OR 'cervical' OR 'board' **The Cochrane Library** (systematic reviews) using the following search term: MeSH descriptor: [spinal injury] explode all trees **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Spinal injury"] OR ((cercival:ti,ab,kw OR spinal:ti,ab,kw) AND injur*:ti,ab,kw) 2. "backboard":ti,ab,kw OR "mattress":ti,ab,kw OR 'spine board':ti,ab,kw OR "vacuum":ti,ab,kw OR "log roll":ti,ab,kw OR [mh "Patient Transfer"] 3. #1 and #2 **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Cervical Vertebrae/injuries"[Mesh] OR "Spinal Cord Injuries"[Mesh] OR ((cervical[TIAB] OR spinal[TIAB]) AND injur*[TIAB]) 2. backboard [TIAB] OR "spine board"[TIAB] OR vacuum [TIAB] OR padded [TIAB] OR mattress [TIAB] OR "Immobilization" [Mesh] OR "Transportation of Patients"[Mesh] OR "log roll"[TIAB] OR "patient transport"[TIAB] OR "6-plus-person"[TIAB] OR 6PP[TIAB] 3. 1 AND 2 **Embase** (via Embase.com interface) using the following search strategy: 1. 'spinal cord injury'/exp OR 'cervical spine'/exp OR ((cervical:ab,ti OR spinal:ab,ti) AND injur*:ab,ti) 2. 'fracture immobilization'/exp OR 'backboard':ab,ti OR 'spine board':ab,ti OR 'vacuum':ab,ti OR 'mattress':ab,ti OR 'stretcher':ab,ti OR 'padded':ab,ti OR 'splint':ab,ti OR ('patient transport'/exp OR 'patient transport':ab,ti OR 'log roll':ab,ti OR '6-plus-person':ab,ti) 3. 1 AND 2 Selected articles were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	02 July 2015
In/Exclusion criteria	**Population**: We included studies with healthy volunteers or trauma victims. **Intervention**: Include: vacuum mattress applied by lay people Exclude: devices which are only used in emergency departments (such as special types of mattresses). **Comparison**: Include: vacuum mattress applied by professional first aid responders **Outcome**: Include: studies measuring time and ease of application Exclude: studies measuring physical outcomes **Study design** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available.

	An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year:** Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Spine injury – Log roll on backboard vs scoop stretcher

Question (PICO)	In patients with a spine injury (P) is a log roll on a backboard (I) better than a scoop stretcher (C) to minimalize spine movement (O)?
Search Strategy	Databases **GIN, NGC** (guidelines) using the search terms 'spine injury' OR 'cervical injury' OR 'backboard' OR 'spine board' OR 'vacuum mattress' **BestBET** (best evidence topics) using the search terms: 'spine' OR 'cervical' OR 'board' OR 'logroll' **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Spinal injury"] OR ((cercival:ti,ab,kw OR spinal:ti,ab,kw) AND injur*:ti,ab,kw) 2. "backboard":ti,ab,kw OR "mattress":ti,ab,kw OR 'spine board':ti,ab,kw OR "vacuum":ti,ab,kw OR "log roll":ti,ab,kw OR [mh "Patient Transfer"] 3. #1 and #2 **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Cervical Vertebrae/injuries"[Mesh] OR "Spinal Cord Injuries"[Mesh] OR ((cervical[TIAB] OR spinal[TIAB]) AND injur*[TIAB]) 2. backboard [TIAB] OR "spine board" [TIAB] OR vacuum [TIAB] OR padded [TIAB] OR mattress [TIAB] OR "Immobilization" [Mesh] OR "Transportation of Patients"[Mesh] OR "log roll"[TIAB] OR "patient transport"[TIAB] OR "6-plus-person"[TIAB] OR 6PP[TIAB] 3. 1 AND 2 **Embase** (via Embase.com interface) using the following search strategy: 1. 'spinal cord injury'/exp OR 'cervical spine'/exp OR ((cervical:ab,ti OR spinal:ab,ti) AND injur*:ab,ti) 2. 'fracture immobilization'/exp OR 'backboard':ab,ti OR 'spine board':ab,ti OR 'vacuum':ab,ti OR 'mattress':ab,ti OR 'stretcher':ab,ti OR 'padded':ab,ti OR 'splint':ab,ti OR ('patient transport'/exp OR 'patient transport':ab,ti OR 'log roll':ab,ti OR '6-plus-person':ab,ti)

	3. 1 AND 2 Systematic reviews used as source for individual studies: Ahn H 2011, Pre-hospital care management of a potential spinal cord injured patient: a systematic review of the literature and evidence-based guidelines
Search date	02 July 2015
In/Exclusion criteria	**Population**: We included studies with cadavers and healthy individuals. **Intervention:** We included studies looking at the log roll in the context of transferring a patient on and of a backboard. We excluded studies comparing techniques used in hospital settings (patient transfer on a surgical table, mechanical devices). **Comparison:** transferring patient on a scoop stretcher **Outcome:** Include: survival, functional recovery, pain, motion, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Study design** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year:** Include: all years

Characteristics of included studies

Author, year	Study design	Population	Comparison	Remarks
Krell, 2006, USA	Experimental: Randomized controlled trial (within subjects design)	31 healthy volunteers (qualified individuals)	Motion in the sagittal, lateral and axial planes when using log roll and backboard vs scoop stretcher	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Motion (°) at Nasion (Na) C3 T12 a)Sagittal flexion b)Axial rotation c)Lateral flexion During 1. application 2. secured roll 3. lift	log-roll (LR) manoeuvre on backboard vs scoop stretcher	1. application a) Sagittal flexion Statistically significant: Na: 9.5±4.9 vs 1.8±1.1 £ (p<0.002) C3: 10.4±5.1 vs 3.0±1.4 £ (p<0.002) T12:12.0±6.4 vs 4.0±3.0 £ (p<0.002) *In favour of scoop stretcher* b) Axial rotation Statistically significant: Na: 8.8±4.8 vs 2.0±1.5 £ (p<0.002)	1, 31 vs 31 § (within subjects design)	Krell 2006

		C3: 10.9±5.4 vs 3.0±2.0 £ (p<0.002) *In favour of scoop stretcher* Not statistically significant : T12:11.8±7.8 vs 6.4±4.7 £† (p>0.05) c) Lateral flexion <u>Statistically significant:</u> Na: 7.5±3.7 vs 1.9±1.3 £ (p<0.002) C3: 9.0±4.6 vs 2.7±1.7 £ (p<0.002) T12: 9.3±4.5 vs 2.2±1.1 £ (p<0.002) *In favour of scoop stretcher* <u>2. secured roll</u> Not statistically significant: a) sagittal flexion Na: 4.2±2.1 vs 4.0±1.7 C3: 3.5±1.9 vs 4.4±2.2 T12: 2.9±1.3 vs 5.6±3.5 (p>0.05) £† b) axial rotation No data available, not measurable † c) lateral flexion Not statistically significant: Na: 3.8±1.3 vs 2.9±1.4 C3: 4.8±1.6 vs 4.3±2.1 T12: 7.8±3.9 vs 6.4±3.3 (p>0.05) £† <u>3. lift</u> a) sagittal flexion <u>Statistically significant:</u> Na: 3.5±1.5 vs 4.7±1.5 £ (p<0.002) *In favour of backboard* Not statistically significant: C3: 3.3±1.2 vs 4.0±1.3 £† (p>0.05) <u>Statistically significant:</u> T12: 2.9±1.3 vs 5.6±3.5 £ (p<0.002) *In favour of backboard* b) axial rotation Not statistically significant: Na: 5.5±3.4 vs 6.0±1.5 C3: 7.9±4.7 vs 6.3±3.4		

		T12: 8.8±4.9 vs 8.3±5.0 (p>0.05) £† c) lateral flexion Not statistically significant: Na: 2.1±0.7 vs 2.1±0.9 C3: 2.2±0.9 vs 2.4±1.2 T12: 2.2±1.2 vs 3.1±1.4 (p>0.05) £†		
Security feeling (100mm scale; 100=most secure) 1. roll 2. lift		<u>1. roll</u> <u>Statistically significant:</u> 59±21 vs 74±13 £ (p=0.003) *In favour of scoop stretcher* <u>2. lift</u> Not statistically significant 79±13 vs 79±17 £† (p=1.00)		
Comfort (100mm scale; 100=most comfortable)		<u>Statistically significant:</u> 58±16 vs 75±13 £ (p<0.001) *In favour of scoop stretcher*		

Mean ± SD (unless otherwise indicated)
£ No CI available
† Imprecision (lack of data)
§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Krell, 2006	Unclear, not specified in the article	Yes, true blinding was impossible, impact unclear	No	No	Cross-over trial; small number of participants; use of healthy volunteers

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample size/lack of data
Inconsistency	0	
Indirectness	-1	Use of cadavers/healthy individuals
Publication bias	-1	COI: One study was supported by Ferno (producing scoop stretchers)
QUALITY (GRADE)	**Final grading Very Low [D]**	

Conclusion	**<u>Motion</u>** (at C5-C6/ at nasion, C3 and T12) **<u>during application:</u>** There is limited evidence from 1 experimental study in favour of using a scoop stretcher. It was shown that the scoop stretcher resulted in a statistically significant decrease of motion during application, compared to the backboard (Krell 2006). Evidence is of very low quality and results cannot be considered precise due to limited sample size. **<u>Motion</u>** (at nasion, C3 and T12) **<u>during secured roll:</u>**

	There is limited evidence neither in favour of the intervention nor the control. A statistically significant decrease of motion, using secured roll compared to the scoop stretcher, could not be demonstrated (Krell 2006). Evidence is of very low quality and results of this study/these studies are imprecise due to limited sample size and/or lack of data. **Motion** (at nasion, C3 and T12) **during lift:** There is limited evidence from 1 experimental study in favour of using a backboard. In making this evidence conclusion, we place a higher value on the significant outcomes over the not significant outcomes. It was shown that the backboard resulted in a statistically significant decrease of motion during lift (for sagittal flexion at nasion and T12), compared to the scoop stretcher (Krell 2006). However, a statistically significant decrease of motion during lift (for axial rotation and lateral flexion), using backboard compared to scoop stretcher, could not be demonstrated (Krell 2006). Evidence is of very low quality and results cannot be considered precise due to limited sample size. **Security feeling:** There is limited evidence from 1 experimental study in favour of scoop stretcher. In making this evidence conclusion, we place a higher value on the significant outcome over the not significant outcome. It was shown that backboard resulted in a statistically significant decrease of security feeling during roll, compared to scoop stretcher (Krell 2006). However, a statistically significant decrease of security feeling during lift, using backboard compared to scoop stretcher, could not be demonstrated (Krell 2006). Evidence is of very low quality and results cannot be considered precise due to limited sample size. **Comfort:** There is limited evidence from 1 experimental study in favour of scoop stretcher. It was shown that backboard resulted in a statistically significant decrease of comfort, compared to scoop stretcher (Krell 2006). Evidence is of very low quality and results cannot be considered precise due to limited sample size.
Reference(s)	**Articles** Krell JM, McCoy MS, Sparto PJ, Fisher GL, Stoy WA, Hostler DP. *Comparison of the Ferno Scoop Stretcher with the long backboard for spinal immobilization.* Prehosp Emerg Care. 2006, 10(1):46-51.

Spine injury – log roll vs sliding/lifting (First Aid)

Question (PICO)	In patients with a spine injury (P) is a log roll (I) compared to sliding/lifting (C) a better way to minimalize spine movement (O)?
Search Strategy	Databases **GIN, NGC** (guidelines) using the search terms 'spine injury' OR 'cervical injury' OR 'backboard' OR 'spine board' OR 'vacuum mattress' **BestBET** (best evidence topics) using the search terms: 'spine' OR 'cervical' OR 'board' OR 'logroll' **The Cochrane Library** (systematic reviews) using the following search terms: MeSH descriptor: [Spinal Injury] explode all trees MeSH descriptor: [Patient Transfer] explode all trees

	The Cochrane Library (controlled trials) using the following search strategy: 1. [mh "Spinal injury"] OR ((cercival:ti,ab,kw OR spinal:ti,ab,kw) AND injur*:ti,ab,kw) 2. "backboard":ti,ab,kw OR "mattress":ti,ab,kw OR 'spine board':ti,ab,kw OR "vacuum":ti,ab,kw OR "log roll":ti,ab,kw OR [mh "Patient Transfer"] 3. #1 and #2 **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Cervical Vertebrae/injuries"[Mesh] OR "Spinal Cord Injuries"[Mesh] OR ((cervical[TIAB] OR spinal[TIAB]) AND injur*[TIAB]) 2. backboard [TIAB] OR 'spine board' [TIAB] OR vacuum [TIAB] OR padded [TIAB] OR mattress [TIAB] OR "Immobilization" [Mesh] OR "Transportation of Patients"[Mesh]OR "log roll"[TIAB] OR "patient transport"[TIAB] OR "6-plus-person"[TIAB] OR 6PP[TIAB] 3. 1 AND 2 **Embase** (via Embase.com interface) using the following search strategy: 1. 'spinal cord injury'/exp OR 'cervical spine'/exp OR ((cervical:ab,ti OR spinal:ab,ti) AND injur*:ab,ti) 2. 'fracture immobilization'/exp OR 'backboard':ab,ti OR 'spine board':ab,ti OR 'vacuum':ab,ti OR 'mattress':ab,ti OR 'stretcher':ab,ti OR 'padded':ab,ti OR 'splint':ab,ti OR ('patient transport'/exp OR 'patient transport':ab,ti OR 'log roll':ab,ti OR '6-plus-person':ab,ti) 3. 1 AND 2 Systematic reviews used as source for individual studies: Ahn H 2011, Pre-hospital care management of a potential spinal cord injured patient: a systematic review of the literature and evidence-based guidelines
Search date	2 July 2015
In/Exclusion criteria	**Population**: We included studies with healthy volunteers and cadavers. **Intervention**: We included studies looking at the log roll, in the context of transferring a patient on and of a backboard. We excluded studies comparing techniques used in hospital settings (patient transfer on a surgical table, mechanical devices). **Comparison:** sliding and lifting techniques, in the context of transferring a patient on and of a backboard. **Outcome:** Include: survival, functional recovery, pain, motion, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Study design** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year:** Include: all years

Characteristics of included studies

Author, year	Study design	Population	Comparison	Remarks
Del Rossi, 2003, USA	Experimental: Randomized controlled trial (within subjects design)	healthy individuals	log-roll (LR) maneuver vs lift-and-slide (LS) technique performed by 48 individuals, 4 teams of 6 qualified individuals trained for log roll, 4 teams of 6 qualified individuals trained for lift and slide	
Del Rossi, 2004, USA	Experimental: Randomized controlled trial (within subjects design)	5 cadavers (2 male, 3 female; mean age 78.8±3.3 years) having created injuries at the C5–C6 level of the spine	log-roll (LR) maneuver vs lift-and-slide (LS) technique performed by 4 teams of 6 qualified individuals	
Del Rossi, 2008a, USA	Experimental: Randomized controlled trial (within subjects design)	5 fresh cadavers (3 males, 2 females; mean age 86.2±11.4 years) having created injuries at the C5–C6 level of the spine	log-roll (LR) maneuver vs lift-and-slide (LS) technique vs 6-plus-person (6PP) lift performed by 1 team of 8 medical professionals	
Del Rossi, 2008b, USA	Experimental: Randomized controlled trial (within subjects design)	5 fresh cadavers (mean age 86.2±11.4 years) with creation of injuries causing instability at the T12–L2 spinal level	log-roll (LR) maneuver vs lift-and-slide (LS) technique vs 6-plus-person (6PP) lift performed by 1 team of 8 qualified individuals	
Horodyski, 2011, USA	Experimental: Randomized controlled trial (within subjects design)	5 cadavers having created injuries at the C5–C6 level of the spine.	log-roll (LR) maneuver vs lift-and-slide (LS) technique performed by 1 team of 4 qualified individuals (log-roll) and 1 team of 8 qualified individuals (lift-and-slide technique)	
Prasarn, 2012a, USA	Experimental: Non-Randomized controlled trial (within subjects design)	5 fresh cadavers (average specimen age 81 years) having created injuries at the C5–C6 level of the spine.	log-roll (LR) maneuver vs 6-plus-person (6PP) lift technique performed by 1 medical team	
Prasarn, 2012b, USA	Experimental: Non-Randomized controlled trial (within subjects design)	Five fresh cadavers having surgically created unstable L-1 burst fracture	log-roll (LR) maneuver vs 6-plus-person (6PP) lift technique performed by 1 medical team	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Flexion-extension motion (°) at C5-C6 level	log-roll (LR) manoeuvre vs lift-and-slide (LS) technique	Not statistically significant: 3.6±2.3 vs 3.3±1.6 λ MD: 0.3 £† (p>0.05)	1, 5 vs 5 § (within subjects design)	Horodyski 2011
		Not statistically significant: Log-roll trained: 9.49±2.06 vs 6.54±0.93 MD: 2.95 £† (p=0.34) Not statistically significant: lift-and-slide trained: 14.25±1.89 vs 7.04±2.72 MD: 7.21 £† (p=0.34)	1, 4 vs 4 § (number of teams performing replacements) (within subjects design)	Del Rossi 2003
		Not statistically significant: 3.92±2.44 vs 3.69±2.80 MD:0.23 £† (p>0.05)	1, 60 vs 60 § (total number of replacements) (within subjects design)	Del Rossi 2004
		Not statistically significant : 5.4±0.6 vs 6.5±0.8 λ MD: -1.1 £† (p>0.05)	1, 5 vs 5 § (within subjects design)	Del Rossi 2008a
	log-roll (LR) manoeuvre vs 6-plus-person lift technique (6PP)	Not statistically significant: 5.4±0.6 vs 6.0±0.8 λ MD: -0.6 £† (p>0.05)		
		a) Spine board placement: Not statistically significant: 11.9±5.0 vs 9.5±4.1 λλ MD: 2.4 £† (p<0.237) b) Transfer to gurney Not statistically significant: 2.2±1.25 vs 1.7±1.0 λλ MD: 0.5 £† (p<0.293) c) Spine board removal Not statistically significant: 9.1±1.8 vs 8.6±3.5 λλ MD: 0.5 £† (p<0.058)	1, 5 vs 5 § (within subjects design)	Prasarn 2012a
Axial-rotation motion (°) at C5-C6 level	Log-roll (LR) manoeuvre vs lift-and-slide (LS) technique	Statistically significant: 3.1±1.9 vs 1.1±0.9 λ MD: 2.0 £ (p<0.05) *In favour of lift-and-slide technique*	1, 5 vs 5 § (within subjects design)	Horodyski 2011
		Statistically significant: Log-roll trained: 24.68±6.24 vs 4.95±1.03 MD: 19.73 £ (p=0.03) *In favour of lift-and-slide technique* Statistically significant: lift-and-slide trained: 20.91±7.70 vs 6.00±1.49 MD: 14.91 £ (p=0.03) *In favour of lift-and-slide technique*	1, 4 vs 4 § (number of teams performing replacements) (within subjects design)	Del Rossi 2003
		Statistically significant : 7.21±0.73 vs 2.01±0.37 MD: 5.2 £ (p=0.008)	1, 5 vs 5 § (within subjects design)	Del Rossi 2008a

		In favour of lift-and-slide technique		
	log-roll (LR) manoeuvre vs 6-plus-person lift technique (6PP)	<u>Statistically significant:</u> 7.21±0.73 vs 2.73±0.33 MD: 4.48 £ (p=0.001) *In favour of 6PP*		
		a) Spine board placement <u>Statistically significant:</u> 7.5±2.6 vs 3.6±0.8 λλ MD: 3.9 £ (p=0.015) *In favour of 6PP* b) Transfer to gurney Not statistically significant: 1.8±2.3 vs 0.9±0.8 λλ MD: 0.9 £† (p=0.241) c) Spine board removal Not statistically significant: 5.8±3.2 vs 3.2±1.2 λλ MD: 2.6 £† (p=0.058)	1, 5 vs 5 § (within subjects design)	Prasarn 2012a
Lateral flexion motion (°) at C5-C6 level	Log-roll (LR) manoeuvre vs lift-and-slide technique	<u>Statistically significant:</u> 3.1±1.6 vs 2.0±2.0 λ MD: 1.1 £ (p<0.05) *In favour of lift-and-slide technique*	1, 5 vs 5 § (within subjects design)	Horodyski 2011
		<u>Statistically significant:</u> Log-roll trained: 12.22±3.48 vs 2.96±0.46 MD: 9.26 £ (p=0.03) *In favour of lift-and-slide technique* <u>Statistically significant:</u> lift-and-slide trained: 17.94±5.78 vs 4.11±0.98 MD: 13.83 £ (p=0.03) *In favour of lift-and-slide technique*	1, 4 vs 4 § (number of teams performing replacements) (within subjects design)	Del Rossi 2003
		<u>Statistically significant :</u> 7.50±0.37 vs 2.58±0.31 MD: 4.92 £ (p=0.003) *In favour of lift-and-slide technique*	1, 5 vs 5 § (within subjects design)	Del Rossi 2008a
	log-roll (LR) manoeuvre vs 6-plus-person lift technique (6PP)	<u>Statistically significant:</u> 7.50±0.73 vs 2.35±0.26 MD: 5.15 £ (p=0.005) *In favour of 6PP*		
		a) Spine board placement: <u>Statistically significant:</u> 8.7±1.5 vs 5.2±2.5 λλ MD: 3.5 £ (p<0.004) *In favour of 6PP* b) Transfer to gurney Not statistically significant: 1.8±2.4 vs 0.7±0.8 λλ MD: 1.1 £† (p=0.195) c) Spine board removal <u>Statistically significant:</u> 6.7±1.9 vs 4.3±2.0 λλ MD: 2.4 £ (p<0.009)	1, 5 vs 5 § (within subjects design)	Prasarn 2012a

		In favour of 6PP		
Anterior-posterior translation (cm) at C5-C6 level	Log-roll (LR) manoeuvre vs lift-and-slide (LS) technique	Statistically significant: 0.40±0.31 vs 0.18±0.16 λ MD: 0.22 £ (p<0.05) *In favour of lift-and-slide technique*	1, 5 vs 5 § (within subjects design)	Horodyski 2011
		Not statistically significant: 0.41±0.06 vs 0.51±0.09 λ MD: -0.10 £† (p>0.05) Data extracted from figure	1, 5 vs 5 § (within subjects design)	Del Rossi 2008a
	log-roll (LR) manoeuvre vs 6-plus-person lift technique (6PP)	Not statistically significant: 0.41±0.06 vs 0.33±0.06 λ MD: 0.08 £† (p>0.05)		
Distraction motion (axial translation) (cm) at C5-C6 level	Log-roll (LR) manoeuvre vs lift-and-slide technique	Not statistically significant: 2.7±1.4 vs 3.1±2.7 λ MD: -0.4 £† (p>0.05)	1, 5 vs 5 § (within subjects design)	Horodyski 2011
		Not statistically significant: 0.51±0.75 vs 0.53±0.11 λ MD: -0.02 £† (p>0.05)	1, 5 vs 5 § (within subjects design)	Del Rossi 2008a
	log-roll (LR) manoeuvre vs 6-plus-person lift technique (6PP)	Not statistically significant: 0.51±0.75 vs 0.33±0.05 λ MD: 0.18 £† (p>0.05)		
Medial-lateral translation (cm) at C5-C6 level	Log-roll (LR) manoeuvre vs lift-and-slide technique	Statistically significant: 0.33±0.20 vs 0.13±0.09 MD: 0.20 £† p<0.05 *In favour of lift-and-slide technique* Data extracted from figure	1, 5 vs 5 § (within subjects design)	Horodyski 2011
		Statistically significant: 0.63±0.06 vs 0.17±0.02 MD: 0.46 £† (p=0.04) *In favour of 6PP*	1, 5 vs 5 § (within subjects design)	Del Rossi 2008a
	log-roll (LR) manoeuvre vs 6-plus-person lift technique (6PP)	Statistically significant: 0.63±0.06 vs 0.17±0.02 MD: 0.46 £† (p=0.02) *In favour of 6PP*		
Flexion-extension motion (°) at T12-L2 level	log-roll manoeuvre (LR) vs 6-plus-person lift technique (6PP)	a) Spine board placement Not statistically significant: 12.6 vs 9.2 MD: 3.4 £† (p=0.29) b) Transfer to gurney Not statistically significant: 1.4 vs 1.4 MD: 2.0 £† (p=0.15) c) Spine board removal Statistically significant: 18.3 vs 8.1 MD: 10.2 £ (p=0.014) *In favour of 6PP*	1, 5 vs 5 § (within subjects design)	Prasarn 2012b
		Not statistically significant: 8.0±2.9 vs 4.4±1.3 MD: 3.6 £† (p>0.05)	1, 5 vs 5 § (within subjects design)	Del Rossi, 2008b

	Log-roll manoeuvre vs lift-and-slide technique	Not statistically significant: 8.0±2.9 vs 6.9±3.3 MD: 1.1 £† (p>0.05)		
Axial-rotation motion (°) at T12-L2 level	log-roll manoeuvre (LR) vs 6-plus-person lift technique (6PP)	a) Spine board placement <u>Statistically significant</u>: 25.2 vs 12.5 MD: 12.7 £ (p=0.018) *In favour of 6PP* b) Transfer to gurney Not statistically significant: 4.5 vs 1.3 MD: 3.2 £† (p=0.19) c) Spine board removal Not statistically significant: 17.7 vs 9.4 MD: 8.3 £† (p=0.09)	1, 5 vs 5 § (within subjects design	Prasarn 2012b
		Not statistically significant: 10.0±2.7 vs 6.9±1.3 MD: 3.1 £† (p>0.05)	1, 5 vs 5 § (within subjects design)	Del Rossi 2008b
	Log-roll manoeuvre vs lift-and-slide technique	<u>Statistically significant:</u> 10.0±2.7 vs 3.6±1.8 MD: 6.4 £ (p=0.001) *In favour of lift-and-slide technique*		
Lateral flexion motion (°) at T12-L2 level	log-roll manoeuvre (LR) vs 6-plus-person lift technique (6PP)	a) Spine board placement <u>Statistically significant:</u> 10.1 vs 5.1 MD: 5.0 £ (p=0.003) *In favour of 6PP* b) Transfer to gurney Not statistically significant: 1.7 vs 0.7 MD: 1.0 £† (p=0.16) c) Spine board removal Not statistically significant: 10.5 vs 5.7 MD: 4.8 £† (p=0.06)	1, 5 vs 5 § (within subjects design)	Prasarn 2012b
		Not statistically significant: 6.7±3.8 vs 2.7±0.5 MD: 4.0 £† (p>0.05)	1, 5 vs 5 § (within subjects design)	Del Rossi, 2008b
	Log-roll manoeuvre vs lift-and-slide technique	Not statistically significant: 6.7±3.8 vs 3.1±1.4 MD: 3.6 £† (p>0.05)		

Mean ± SD (unless otherwise indicated)
£ CI not available
† Imprecision (lack of data)
§ Imprecision (limited sample size or low number of events)
λ data extracted from graph
λλ SD extracted from graph

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Del Rossi, 2003	Unclear, not specified in the article	Yes, impact unclear	No	No	Cross-over trial; small number of participants; use of healthy volunteers
Del Rossi, 2004	Unclear, not specified in the article	Yes, impact unclear	No	No	Cross-over trial; small number of replacements
Del Rossi, 2008a	Unclear, not specified in the article	Yes, impact unclear	No	No	Cross-over trial; small number of replacements
Del Rossi, 2008b	Unclear, not specified in the article	Yes, impact unclear	No	No	Cross-over trial; small number of replacements
Horodyski, 2011	Unclear, not specified in the article	Yes, impact unclear	No	No	Cross-over trial; small number of replacements
Prasarn, 2012a	Yes	Yes, impact unclear	No	No	Cross-over trial; No randomization; small number of replacements
Prasarn, 2012b	Unclear, not specified in the article	Yes, impact unclear	No	No	Cross-over trial; small number of replacements

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/lack of data
Inconsistency	0	
Indirectness	-1	Use of healthy volunteers or cadavers
Publication bias	0	
QUALITY (GRADE)	**Final grading Very Low [D]**	

Conclusion	**Motion at C5-C6:** There is limited evidence from 5 experimental studies in favour of lift-and-slide technique/6 plus person lift technique. In making this evidence conclusion, we place a higher value on statistically significant outcomes over non-significant outcomes. It was shown that the log-roll maneuver resulted in a statistically significant increase of **axial rotation motion and lateral flexion motion,** compared to lift-and-slide technique/6 plus person lift technique (Del Rossi 2003, Del Rossi 2004, Del Rossi 2008a, Horodyski 2011, Prasarn 2012a). It was shown that the log-roll maneuver resulted in a statistically significant increase of **anterior-posterior translation and medial-lateral translation**, compared to lift-and-slide technique/6 plus person lift technique (Del Rossi 2008a, Horodyski 2011). A statistically significant decrease of **anterior-posterior translation**, using the log-roll manoeuvre compared to 6 plus person lift technique, could not be demonstrated (Del Rossi 2008a). Also, a statistical significant decrease of **axial rotation motion** (during transfer to gurney or spinal board removal) and **lateral flexion motion** (during transfer to gurney), using the log-roll manoeuvre compared to 6 plus person lift technique for transfer to gurney and spinal board removal, could not be demonstrated (Prasarn 2012a). Furthermore, a statistically significant decrease of **flexion-extension motion** and **axial translation**, using the log-roll manoeuvre compared to lift-and-slide technique/6 plus person lift technique, could not be demonstrated (Del Rossi 2003, Del Rossi 2004, Del Rossi 2008a, Horodyski 2011, Prasarn 2012a).

	Evidence is of very low quality and results cannot be considered precise due to limited sample size and/or lack of data. **Motion at T12-L2:** There is limited evidence from 2 experimental studies in favour of lift-and-slide technique/6 plus person lift technique. In making this evidence conclusion, we place a higher value on statistically significant outcomes over non-significant outcomes. It was shown that the log-roll maneuver resulted in a statistically significant increase of **flexion-extension motion** (during spinal board removal)**,** compared to 6 plus person lift technique (Prasarn 2012b). It was also shown that the log-roll maneuver resulted in a statistically significant increase of **axial-rotation motion,** compared to lift-and-slide technique (Del Rossi 2008b). Furthermore, it was shown that the log-roll maneuver resulted in a statistically significant increase of **lateral flexion motion,** compared to 6 plus person lift technique (Prasarn 2012b, Del Rossi 2008b). However, a statistically significant decrease of **flexion-extension** (during spine board placement and transfer to gurney), **axial-rotation motion** (during spine board placement, transfer to gurney and spine board removal) and **lateral flexion motion** (during transfer to gurney and spine board removal), using the log-roll manoeuvre compared to 6 plus person lift technique, could not be demonstrated (Prasarn 2012b, Del Rossi 2008b). Also, a statistically significant decrease of **flexion-extension** and **lateral flexion motion**, using the log-roll manoeuvre compared to lift-and-slide technique, could not be demonstrated (Del Rossi 2008b).
Reference(s)	**Articles** Del Rossi G, Horodyski M, Powers ME. *A Comparison of Spine-Board Transfer Techniques and the Effect of Training on Performance*. J Athl Train. 2003, 38(3):204-208. Del Rossi G, Horodyski M, Heffernan TP, Powers ME, Siders R, Brunt D, Rechtine GR. *Spine-board transfer techniques and the unstable cervical spine*. Spine (Phila Pa 1976). 2004, 29(7):E134-138. Del Rossi G, Horodyski MH, Conrad BP, Di Paola CP, Di Paola MJ, Rechtine GR. *The 6-plus-person lift transfer technique compared with other methods of spine boarding*. J Athl Train. 2008a, 43(1):6-13 Del Rossi G, Horodyski M, Conrad BP, Dipaola CP, Dipaola MJ, Rechtine GR. *Transferring patients with thoracolumbar spinal instability: are there alternatives to the log roll maneuver?* Spine (Phila Pa 1976). 2008b, 33(14):1611-1615 Horodyski M, Conrad BP, Del Rossi G, DiPaola CP, Rechtine GR 2nd. *Removing a patient from the spine board: is the lift and slide safer than the log roll?* J Trauma. 2011, 70(5):1282-1285 Prasarn ML, Horodyski M, Dubose D, Small J, Del Rossi G, Zhou H, Conrad BP, Rechtine GR. *Total motion generated in the unstable cervical spine during management of the typical trauma patient: a comparison of methods in a cadaver model*. Spine. 2012a, 37(11):937-942. Prasarn ML, Zhou H, Dubose D, Rossi GD, Conrad BP, Horodyski M, Rechtine GR. *Total motion generated in the unstable thoracolumbar spine during management of the typical trauma patient: a comparison of methods in a cadaver model.* J Neurosurg Spine. 2012b, 16(5):504-508 **Systematic reviews** Ahn H, Singh J, Nathens A, MacDonald RD, Travers A, Tallon J, Fehlings MG, Yee A. *Pre-hospital care management of a potential spinal cord injured patient: a systematic review of the literature and evidence-based guidelines*. J Neurotrauma. 2011, 28(8):1341-1361.

Spine injury – Padded vs unpadded backboard (First Aid)

Question (PICO)	In patients requiring spinal immobilization (P) is a padded backboard (I) better than an unpadded backboard (C) at providing comfort and immobilization (O)?
Search Strategy	Databases **GIN, NGC** (guidelines) using the search terms 'spine injury' OR 'cervical injury' OR 'backboard' OR 'spine board' OR 'vacuum mattress' **BestBET** (best evidence topics) using the search terms: 'spine' OR 'cervical' OR 'board' **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Spinal injury"] OR ((cercival:ti,ab,kw OR spinal:ti,ab,kw) AND injur*:ti,ab,kw) 2. "backboard":ti,ab,kw OR "mattress":ti,ab,kw OR 'spine board':ti,ab,kw OR "vacuum":ti,ab,kw OR "log roll":ti,ab,kw OR [mh "Patient Transfer"] 3. #1 and #2 **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Cervical Vertebrae/injuries"[Mesh] OR "Spinal Cord Injuries"[Mesh] OR ((cervical[TIAB] OR spinal[TIAB]) AND injur*[TIAB]) 2. backboard [TIAB] OR "spine board"[TIAB] OR vacuum [TIAB] OR padded [TIAB] OR mattress [TIAB] OR "Immobilization" [Mesh] OR "Transportation of Patients"[Mesh] OR "log roll"[TIAB] OR "patient transport"[TIAB] OR "6-plus-person"[TIAB] OR 6PP[TIAB] 3. 1 AND 2 **Embase** (via Embase.com interface) using the following search strategy: 1. 'spinal cord injury'/exp OR 'cervical spine'/exp OR ((cervical:ab,ti OR spinal:ab,ti) AND injur*:ab,ti) 2. 'fracture immobilization'/exp OR 'backboard':ab,ti OR 'spine board':ab,ti OR 'vacuum':ab,ti OR 'mattress':ab,ti OR 'stretcher':ab,ti OR 'padded':ab,ti OR 'splint':ab,ti OR ('patient transport'/exp OR 'patient transport':ab,ti OR 'log roll':ab,ti OR '6-plus-person':ab,ti) 3. 1 AND 2 Systematic reviews used as source for individual studies: Ahmad 2007, BestBET 'Spinal boards or vacuum mattresses for immobilisation'. Ahn H 2011, Pre-hospital care management of a potential spinal cord injured patient: a systematic review of the literature and evidence-based guidelines. Kwan I 2009, Cochrane review: Spinal immobilization for trauma patients. Selected articles were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	02 July 2015
In/Exclusion criteria	**Population:** Healthy volunteers. **Intervention:** Padded backboard **Comparison:** Unpadded backboard **Outcome**: Studies measuring comfort and pain or immobilization. We excluded studies measuring biomechanical markers (respiratory volumes) **Study design** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available.

	An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year:** Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Cordell, 1995, USA	Experimental: Randomized controlled trial (within subjects design)	20 healthy volunteers (12 female, 8 male), mean age 29.9 years (SEM 2.2)	Immobilisation (80 min) on: • Wooden spine board with air mattress • Spine board without mattress Both groups had a cervical collar.	
Edlich, 2011, USA	Experimental: Non-randomized controlled trial (within subjects design)	10 healthy volunteers (5 male, 5 female), mean age 45.3±9.38 years	Immobilisation (15+30 min) on: • Backboard with a Back Raft air mattress system • Backboard without air mattress system	
Hauswald, 2000, USA	Experimental: Randomized controlled trial (within subjects design)	22 healthy volunteers	Immobilisation (10 min) on: • unpadded wooden backboard • backboard padded with a folded blanket • backboard padded with 3cm gurney mattress • backboard padded with 6cm egg crate foam pad	
Lerner, 1998, USA	Experimental: Randomized controlled trial (within subjects design)	39 healthy volunteers (18-65 years)	Immobilisation (15+45 min) on: • Padded wooden backboard • Unpadded wooden backboard	
Lovell, 1994, UK	Experimental: Non-randomized controlled trial (within subjects design)	30 healthy volunteers	Interface pressure (sacral and thoracic) on: • Spinal board • Padded spinal board • Vacuum stretcher [Data for vacuum stretcher were not extracted]	
Sheerin, 2007, Ireland	Experimental: Non-randomized controlled trial (within subjects design)	2 healthy male volunteers, 41 and 23 years old	Interface pressure (sacral and occipital) on: • Spinal board • Padded spinal board • Vacuum stretcher [Data for vacuum stretcher were not extracted]	
Walton, 1994, USA	Experimental: Randomized controlled trial (within subjects design)	30 healthy volunteers (4 women, 26 men), mean age 32.5±7.0 years	Immobilisation (30 min) on: • Foam-padded spine board • Unpadded spine board	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Pain (100 mm unnumbered scale)	spine board with air mattress vs spine board without mattress	Statistically significant: 9.7±2.5 vs 37.5±6.4 MD: -27.8 (p=0.0001) £ *In favour of the air mattress*	1, 20 vs 20 § (within subjects design)	Cordell 1995
Pain (10-point scale; 0=no pain)	padded backboard (with air mattress) vs unpadded backboard	After 15min: Statistically significant: 0.40±0.22 vs 3.15±0.32 MD: -2.75, 95%CI [-2.51;-2.99] (p<0.05) *In favour of padded backboard* After 30 min: Statistically significant: 0.90±0.18 vs 6.00±0.53 MD: -5.10, 95%CI [-5.45;-4.75] (p<0.05) *In favour of padded backboard*	1, 10 vs 10 § (within subjects design)	Edlich 2011
Number of persons with pain symptoms	padded backboard vs unpadded backboard	Not statistically significant: 27/39 vs 30/39 £† RR: 0.90 (p>0.05)	1, 39 vs 39 § (within subjects design)	Lerner 1998
Discomfort (10-point scale; 0=more pain)	padded backboard (6mm) vs padded backboard (3mm) vs padded backboard (blanket) vs unpadded backboard	Statistically significant: 9.6±1.0 vs 7.0±1.1 vs 3.3±2.6 vs 0.8±1.6 λ£ Each intervention from each of the others: (p<0.05) *In favour of more padding*	1, 22 vs 22 § (within subjects design)	Hauswald 2000
	padded backboard vs unpadded backboard	Statistically significant: 2.5±2.1 vs 5.4±4.6 MD: -2.90 (p=0.024) £ *In favour of padded backboard*	1, 30 vs 30 § (within subjects design)	Walton 1994
Sacral interface pressure (mmHg)	spine board with air mattress vs spine board without mattress	Statistically significant: 48.5±5.9 145.5±14.0 MD: -97.0 (p=0.0001) £ *In favour of the air mattress*	1, 20 vs 20 § (within subjects design)	Cordell 1995
	padded (with air mattress) backboard vs unpadded backboard	Statistically significant: 46.20±1.99 vs 60.00±2.27 MD:-13.80 [-15.67;-11.93] (p<0.05) *In favour of padded backboard*	1, 10 vs 10 § (within subjects design)	Edlich 2011
	padded backboard vs unpadded backboard	Statistically significant: 115.5 vs 147.3 MD: -31.8 (p>0.05) £ *In favour of padded backboard*	1, 30 vs 30 § (within subjects design)	Lovell 1994
	padded backboard vs unpadded backboard	Statistically significant: 59.5±23.33 vs 136.33±25.45 MD:-25.58 (p<0.05) £ λλ *In favour of padded backboard*	1, 2 vs 2 § (within subjects design)	Sheerin 2007
Heel interface pressure (mmHg)	spine board with air mattress vs spine board without mattress	Statistically significant: 34.5±1.7 vs 50.0±2.7 MD: -15.5 (p=0.0001) £ *In favour of air mattress*	1, 20 vs 20 § (within subjects design)	Cordell 1995

Thoracic interface pressure (mmHg)	padded backboard vs unpadded backboard	Not statistically significant: 0.0 vs 0.0 MD: 0.0 (p>0.05) £†	1, 30 vs 30 § (within subjects design)	Lovell 1994
Occipital interface pressure (mmHg)	spine board with air mattress vs spine board without mattress	Statistically significant: 29.9±1.2 vs 57.1±2.9 MD: -27.2 (p=0.0001) £ *In favour of air mattress*	1, 20 vs 20 § (within subjects design)	Cordell 1995
	padded (with air mattress) backboard vs unpadded backboard	Statistically significant: 40.20±2.04 vs 55.60±3.09 MD: -15.40 [-17.69;-13.11], (p<0.05) *In favour of padded backboard*	1, 10 vs 10 § (within subjects design)	Edlich 2011
	padded backboard vs unpadded backboard	Statistically significant: 61.67±7.07 vs 87.25±10.96 λλ MD:-76.83 (p<0.05) £† *In favour of padded backboard*	1, 2 vs 2 § (within subjects design)	Sheerin 2007
Scapula interface pressure (mmHg)	padded (with air mattress) backboard vs unpadded backboard	Statistically significant: 36.10±1.41 vs 51.90±1.57 MD: -15.80 [-17.11;-14.49] (p<0.05) *In favour of padded backboard*	1, 10 vs 10 § (within subjects design)	Edlich 2011
Cervical motion, flexion	padded backboard vs unpadded backboard	Not statistically significant: 4.0±1.6 vs 4.0±1.5 MD: 0.0, 95%CI [-0.9; 0.8] (p=0.41)	1, 30 vs 30 § (within subjects design)	Walton 1994
Cervical motion, extension		Not statistically significant: 9.0±5.9 vs 8.8±5.2 MD:0.20, 95%CI [-3.2; 2.6] (p=0.23)		
Cervical motion, rotation (goniometer)		Not statistically significant: 6.3±5.6 vs 7.6±4.9 MD:-1.30, 95%CI [-1.3; 3.8] (p=0.89)		
Cervical motion, rotation (inclinometer)		Not statistically significant: 5.7±4.8 vs 6.7±4.8 MD:-1.0 (p=0.18) £†		
Cervical motion, lateral bending		Not statistically significant: 14.3±5.9 vs 15.6±8.2 MD:-1.2, 95%CI [-2.3; 5.1] (p=0.23)		

Mean ± SD (unless otherwise indicated)
£ No effect size and/or CI available
† Imprecision (lack of data)
§ Imprecision (limited sample size or low number of events)
λ Data extracted from graph
λλ Mean values ± SDs were calculated in Excel

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Cordell, 1995	Unclear, not specified in the article	Yes, participants are doing both interventions and make a self-evaluation	No	No	Block randomization; cross-over study
Edlich, 2011	Yes, no randomization	Yes, participants are doing both interventions and make a self-evaluation	No	No	Within subjects

Hauswald, 2000	Unclear, not specified in the article	Yes, participants are doing both interventions and make a self-evaluation	No	No	Randomization done using a table of random digits; cross-over study
Lerner, 1998	Unclear, not specified in the article	Yes, participants are doing both interventions and make a self-evaluation	No	No	Cross-over study
Lovell 1994	Yes, no randomization	Yes	No	No	Within subjects; the thoracic sensor is not touching the surface on the backboard, no interface pressure can be measured
Sheerin 2007	Yes, no randomization	Yes	No	No	Within subjects

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes
Inconsistency	0	
Indirectness	-1	Studies with healthy individuals
Publication bias	0	
QUALITY (GRADE)	**Final grading Very Low [D]**	

Conclusion	**<u>Pain and discomfort:</u>** There is limited evidence from 5 experimental studies in favour of the padded backboard. It was shown that a padded backboard or air mattress resulted in a statistically significant decrease of pain and discomfort, compared to an unpadded backboard (Cordell 1995, Edlich 2011, Hauswald 2000, Walton 1994). A statistically significant decrease of number of patients with pain, using a padded backboard compared to an unpadded backboard, could not be demonstrated (Lerner 1998). Evidence is of very low quality and results cannot be considered precise due to limited sample size. **<u>Interface pressure:</u>** There is limited evidence from 4 experimental studies in favour of the padded backboard. It was shown that a padded backboard resulted in a statistically significant decrease of sacral, heel, occipital and scapula interface pressure, compared to an unpadded backboard (Cordell 1995, Edlich 2011, Lovell 1994, Sheerin 2007). A statistically significant decrease of thoracic interface pressure, using a padded backboard compared to an unpadded backboard, could not be demonstrated (Lovell 1994). Evidence is of very low quality and results cannot be considered precise due to limited sample size and/or lack of data. **<u>Cervical immobilization:</u>** There is limited evidence from 1 experimental study, neither in favour of the intervention nor the control. A statistically significant decrease of cervical motion, using a padded backboard compared to an unpadded backboard, could not be demonstrated (Walton 1994). Evidence is of very low quality and results of this study are imprecise due to limited sample size.
Reference(s)	**<u>Articles</u>**

	Cordell WH, Hollingsworth JC, Olinger ML, Stroman SJ, Nelson DR. *Pain and tissue-interface pressures during spine-board immobilization.* Ann Emerg Med. 1995, 26(1):31-36. Edlich RF, Mason SS, Vissers RJ, Gubler KD, Thacker JG, Pharr P, Anderson M, Long WB 3rd. *Revolutionary advances in enhancing patient comfort on patients transported on a backboard*. Am J Emerg Med. 2011, 29(2):181-186 Hauswald M, Hsu M, Stockoff C. *Maximizing comfort and minimizing ischemia: a comparison of four methods of spinal immobilization.* Prehosp Emerg Care. 2000, 4(3):250-252. Lerner EB, Billittier AJ 4th, Moscati RM. *The effects of neutral positioning with and without padding on spinal immobilization of healthy subjects*. Prehosp Emerg Care. 1998, 2(2):112-116. Lovell ME, Evans JH. *A comparison of the spinal board and the vacuum stretcher, spinal stability and interface pressure*. Injury. 1994, 25(3):179-180. Sheerin F, de Frein R. *The occipital and sacral pressures experienced by healthy volunteers under spinal immobilization: a trial of three surfaces*. J Emerg Nurs. 2007, 33(5):447-450. Walton R, DeSalvo JF, Ernst AA, Shahane A. *Padded vs unpadded spine board for cervical spine immobilization*. Acad Emerg Med. 1995, 2(8):725-758. **Systematic reviews** Ahmad M, Butler J. *BestBET: Spinal boards or vacuum mattresses for immobilisation.* BestBET 2007 Ahn H, Singh J, Nathens A, MacDonald RD, Travers A, Tallon J, Fehlings MG, Yee A. *Pre-hospital care management of a potential spinal cord injured patient: a systematic review of the literature and evidence-based guidelines.* J Neurotrauma. 2011, 28(8):1341-1361. Kwan I, Bunn F, Roberts IG. *Spinal immobilization for trauma patients*. Cochrane review 2009

Spine injury – Vacuum matress vs backboad (First Aid)

Question (PICO)	In patients requiring spinal immobilization (P) is a vacuum mattress (I) better than a long spinal board (C) at providing comfort and immobilization (O)?
Search Strategy	Databases **GIN, NGC** (guidelines) using the search terms 'spine injury' OR 'cervical injury' OR 'backboard' OR 'spine board' OR 'vacuum mattress' **BestBET** (best evidence topics) using the search terms: 'spine' OR 'cervical' OR 'board' **The Cochrane Library** (systematic reviews) using the following search term: MeSH descriptor: [spinal injury] explode all trees **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Spinal injury"] OR ((cercival:ti,ab,kw OR spinal:ti,ab,kw) AND injur*:ti,ab,kw) 2. "backboard":ti,ab,kw OR "mattress":ti,ab,kw OR 'spine board':ti,ab,kw OR "vacuum":ti,ab,kw OR "log roll":ti,ab,kw OR [mh "Patient Transfer"] 3. #1 and #2 **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Cervical Vertebrae/injuries"[Mesh] OR "Spinal Cord Injuries"[Mesh] OR ((cervical[TIAB] OR spinal[TIAB]) AND injur*[TIAB]) 2. backboard [TIAB] OR "spine board" [TIAB] OR vacuum [TIAB] OR padded [TIAB] OR mattress [TIAB] OR "Immobilization" [Mesh] OR "Transportation of Patients"[Mesh] OR "log roll"[TIAB] OR "patient transport"[TIAB] OR "6-plus-person"[TIAB] OR 6PP[TIAB] 3. 1 AND 2 **Embase** (via Embase.com interface) using the following search strategy:

	1. 'spinal cord injury'/exp OR 'cervical spine'/exp OR ((cervical:ab,ti OR spinal:ab,ti) AND injur*:ab,ti) 2. 'fracture immobilization'/exp OR 'backboard':ab,ti OR 'spine board':ab,ti OR 'vacuum':ab,ti OR 'mattress':ab,ti OR 'stretcher':ab,ti OR 'padded':ab,ti OR 'splint':ab,ti OR ('patient transport'/exp OR 'patient transport':ab,ti OR 'log roll':ab,ti OR '6-plus-person':ab,ti) 3. 1 AND 2 Systematic reviews used as source for individual studies: Ahmad 2007, BestBET 'Spinal boards or vacuum mattresses for immobilisation'. Ahn H 2011, Pre-hospital care management of a potential spinal cord injured patient: a systematic review of the literature and evidence-based guidelines Kwan I 2009, Cochrane review: Spinal immobilization for trauma patients. Selected articles were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	02 July 2015
In/Exclusion criteria	**Population**: We included studies with healthy volunteers or trauma victims. **Intervention**: Include: vacuum mattress Exclude: devices which are only used in emergency departments (such as special types of mattresses). **Comparison**: Include: long spinal board, unpadded backboard **Outcome**: We included studies measuring comfort and pain or immobilization. We excluded studies measuring biomechanical markers (respiratory volumes) **Study design** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year:** Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Chan, 1996, USA	Experimental: Randomized controlled trial (within subjects design)	27 healthy volunteers, aged 17-49 years, without history of back pain/spinal disease	Immobilisation (30min) on: • Wooden backboard • Mattress-splint Both groups also had a StifNeck collar	
Cross, 2001, USA	Experimental: Randomized controlled trial (within subjects design)	18 healthy volunteers (10 female, 8 male), mean age 34 (range 18-54 years), without history of back pain/spinal disease	Immobilisation (60min) on: • Hard spine board • Vacuum splint (model 1) • Vacuum splint (model 2)	sample size was based on results of an earlier study
Hamilton, 1996, USA	Experimental: Randomized controlled trial (within subjects design)	26 healthy volunteers (22 men, 4 women), mean age 28.9±9 years, without history of back/neck pain	Immobilisation on: • Spine board (with/without StifNeck collar)	

			• Mattress-splint (with/without StifNeck collar)	
Johnson, 1996, USA	Experimental: Randomized controlled trial (within subjects design)	30 healthy students (to test comfort) + 30 extra students (to test immobilization)	Immobilisation (30min) on: • Wooden backboard (with/without StifNeck collar) • Mattress-splint (with/without StifNeck collar)	
Keller, 2005, The Netherlands	Experimental: Randomized controlled trial (within subjects design)	20 healthy volunteers, average age 40 years (range 20-56 years) without history of back pain	Immobilisation on: • Spinal board • Vacuum mattress • ER-overlay mattress [data on ER-overlay mattress were not extracted]	
Lovell, 1994, UK	Experimental: Non-randomized controlled trial (within subjects design)	30 healthy volunteers	Immobilisation on: • Spinal board • Padded spinal board • Vacuum stretcher	
Luscombe, 2003, UK	Experimental: Non-randomized controlled trial (within subjects design)	9 healthy volunteers (8 male, 1 female)	Immobilisation on: • Backboard • Vacuum mattress	
Mahshidfar, 2013, Iran	Experimental: randomized controlled trial	60 trauma victims (49 male, 11 female) with possible spinal trauma were randomly assigned to either LBB (n=30), mean age 30.25±2.95 years or VMS (n=30); mean age 35.50±3.13 years	Immobilisation on: • Long backboard (LBB): Spencer Rock plastic backboard stretcher with Spencer contour head immobilizer • Vacuum mattress splint (VMM): Attucho "NYB" vacuum mattress TPU In both cases, the cervical spine was immobilized immediately using a rigid cervical collar.	
Sheerin, 2007, Ireland	Experimental: Non-randomized controlled trial (within subject design)	2 healthy male volunteers, 41 and 23 years old	Interface pressure (sacral and occipital) on: • Spinal board • Padded spinal board • Vacuum stretcher	
Totten, 1999, USA	Experimental: Randomized controlled trial (within subjects design)	39 healthy volunteers (20 male, 19 female), mean age 40.43±26.65 years,	Immobilisation on: • Wooden backboard • Vacuum mattress Both groups were wearing a collar.	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Number of persons with pain symptoms	wooden backboard vs vacuum mattress splint	Statistically significant: 28/37 vs 9/28 § aRR: 3.08, 95%CI [1.74;5.44] (p<0.0001)	1, 37 vs 28 (within subjects design)	Chan 1996

		In favour of vacuum mattress		
	hard spine board vs vacuum splint (model 1) vs vacuum splint (model 2)	After 30 min: <u>Statistically significant:</u> Occiput: 14/18 vs 5/18 vs 6/18 £§ (p<0.01) *In favour of vacuum splints* Lower back: 10/18 vs 1/18 vs 3/18 £§ (p<0.01) *In favour of vacuum splints* Not statistically significant: Neck: 6/18 vs 4/18 vs 1/18 £†§ (p=0.15) Upper back 6/18 vs 3/18 vs 3/18 £†§ (p=0.41) Sacrum: 10/18 vs 7/18 vs 5/18 £†§ (p=0.21) Elbows: 0/18 vs 0/18 vs 1/18 £†§ (p=0.37) Heels/ankles 4/18 vs 1/18 vs 2/18 £†§ (p=0.25) After 60 min: <u>Statistically significant:</u> Occiput: 15/18 vs 6/18 vs 6/18 £§ (p<0.01) *In favour of vacuum splints* Lower back: 7/18 vs 2/18 vs 4/18 £§ (p=0.04) *In favour of vacuum splints* Not statistically significant: Neck: 6/18 vs 4/18 vs 4/18 £†§ (p=0.61) Upper back: 7/18 vs 5/18 vs 7/18 £†§ (p=0.72) Sacrum: 10/18 vs 7/18 vs 5/18 £†§ (p=0.15)	1, 18 vs 18 vs 18 (within subjects design)	Cross 2001

		Elbows: 0/18 vs 0/18 vs 2/18 £†§ (p=0.14) Heels/ankles 4/18 vs 1/18 vs 2/18 £†§ (p=0.25)		
Pain (10-point scale; 0=more pain)	backboard vs vacuum splint	<u>Statistically significant:</u> Median: 6 vs 3 (p<0.001) £ *In favour of vacuum splint*	1, 30 vs 30 § (within subjects design)	Johnson 1996
Discomfort (10-point scale; 0=no discomfort)	backboard vs backboard with Stifneck collar vs vacuum splint vs vacuum splint with Stifneck collar	<u>Statistically significant:</u> 3.4±1.3 vs 3.2±1.4 vs 1.0±0.7 vs 1.2±1.0 £ (p<0.05) *In favour of vacuum splint (with and without Stifneck collar)*	1, 26 vs 26 vs 26 vs 26 § (within subjects design)	Hamilton 1996
Comfort (1-10 scale; 1=no pain)	backboard vs vacuum mattress	<u>Statistically significant:</u> 4.6±1.2 vs 6.6±1.3 MD:-2.00 (p<0.05) £ *In favour of vacuum mattress*	1, 20 vs 20 § (within subjects design)	Keller 2005
	backboard vs vacuum mattress	<u>Statistically significant:</u> 5.22 vs 1.88 MD: 3.34, 95%CI [2.12;4.55] (p<0.01) *In favour of vacuum mattress*	1, 9 vs 9 § (within subjects design)	Luscombe 2003
High patient comfort	long backboard vs vacuum mattress splint	<u>Statistically significant:</u> 16/30 vs 0/30 £§ (p<0.001) *In favour of long backboard*	1, 30 vs 30	Mahshidfar 2013
Comfort (1-6 scale; 1=very uncomfortable)	wooden backboard vs vacuum mattress	<u>Statistically significant:</u> 2.8±1.25 vs 4.8±0.92 MD: -2.00 (p<0.001) £ *In favour of vacuum mattress*	1, 39 vs 39 § (within subjects design)	Totten 1999
Sacral interface pressure (mmHg)	backboard- padded backboard vs vacuum mattress	<u>Statistically significant:</u> 147.3 vs 115.5 vs 36.7 (p<0.05) £ *In favour of vacuum mattress*	1, 30 vs 30 § (within subjects design)	Lovell 1994
	backboard vs vacuum mattress	Not statistically significant: 174.9±15.8 vs 165.6±29.0 MD: 9.30 (p>0.05) £†	1, 20 vs 20 § (within subjects design)	Keller 2005
	backboard vs vacuum mattress	<u>Statistically significant:</u> 136.33±25.45 vs 65.5±7.31 MD:70.83, 95%CI [34.12; 107.54] (p=0.0002) *In favour of vacuum mattress*	1, 2 vs 2 § (within subjects design)	Sheerin 2007
	padded backboard vs vacuum mattress	Not statistically significant: 59.5±23.33 vs 65.5±7.31 MD: -6.00, 95%CI [-39.88; 27.88] (p=0.73) ¥		
Scapulae interface pressure (mmHg)	backboard vs vacuum mattress	<u>Statistically significant</u> 176.6±3.6 vs 131.6±50.9 MD: 45.0 (p<0.05) £	1, 20 vs 20 § (within subjects design)	Keller 2005

		In favour of the vacuum mattress		
Heels interface pressure (mmHg)	backboard vs vacuum mattress	Statistically significant: 153.0±16.1 vs 123.3±45.2 MD:29.70 (p<0.05) £ *In favour of the vacuum mattress*		
Occipital interface pressure (mmHg)	backboard vs vacuum mattress	Statistically significant: 87.25±10.96 vs 59.5±7.77 MD: 28.05, 95%CI [9.42;46.68] (p=0.003) *In favour of vacuum mattress*	1, 2 vs 2 § (within subjects design)	Sheerin 2007
	padded backboard vs vacuum mattress	Not statistically significant: 61.67±7.07 vs 59.5±7.77 MD: 2.47, 95%CI [-12.10;17.04] (p=0.74)		
Immobilization (overall) (10-point scale; 0=more mobile)	Backboard vs backboard with Stifneck collar vs vacuum splint vs vacuum splint with Stifneck collar	Statistically significant: 6.6±1.5 vs 7.5±1.0 vs 7.3±1.0 vs 8.1±1.0 £† (p>0.05) *In favour of vacuum splint with Stifneck collar*	1, 26 vs 26 vs 26 vs 26 § (within subjects design)	Hamilton 1996
Head movement (cm)	Backboard vs vacuum splint	Statistically significant: 2.6±1.1 vs 4.3±1.6 MD:-1.70 (p<0.001) £ *In favour of vacuum splint*	1, 60 vs 60 § (within subjects design)	Johnson 1996
	Backboard with Stifneck collar vs vacuum splint with Stifneck collar	Statistically significant: 2.8±1.1 vs 4.0±1.4 MD:-1.20 (p<0.001) £ *In favour of vacuum splint*		
	backboard vs vacuum mattress	Statistically significant: Head up: 2.330 vs 0.666 MD: 1.664, 95%CI [0.961;3.878] (p<0.01) *In favour of vacuum mattress* Head down: 4.089 vs 0.833 MD: 3.256, 95%CI [1.590;6.920] (p<0.01) *In favour of vacuum mattress* Lateral tilt: 1.833 vs 0.426 MD:1.407, 95%CI [0.666; 2.942] (p<0.01) *In favour of vacuum mattress*	1, 9 vs 9 § (within subjects design)	Luscombe 2003
Shoulder movement (cm)	Backboard vs vacuum splint	Not statistically significant: 4.1±1.7 vs 3.5±1.6 MD: 0.60 (p>0.05) £†	1, 60 vs 60 § (within subjects design)	Johnson 1996
	Backboard with Stifneck collar vs vacuum splint with Stifneck collar	Statistically significant: 4.6±1.6 vs 3.4±1.7 MD:1.20 (p<0.003) £ *In favour of backboard*		
Hip movement (cm)	Backboard vs vacuum splint	Statistically significant: 3.4±1.5 vs 1.3±0.9 MD: 2.10 (p<0.001) £ *In favour of backboard*		

	Backboard with Stifneck collar vs vacuum splint with Stifneck collar	Statistically significant: 3.4±1.6 vs 1.4±1.0 MD: 2.0 (p<0.001) £ *In favour of backboard*		
High Immobilisation	long backboard vs vacuum mattress splint	Statistically significant: Flexion & extension: 17/30 vs 0/30 § RR: 35.0, 95%CI [2.20; 556.71] (p=0.01) * *In favour of long backboard* Lateral bending 13/30 vs 0/30 § RR: 27.0, 95%CI [1.68; 434.53] (p=0.02) * *In favour of long backboard* Rotation 25/30 vs 0/30 § RR: 51.0, 95%CI [3.25; 801.15] (p=0.005) * *In favour of long backboard* Thoraco-lumbar 12/30 vs 0/30 § RR: 25.0, 95%CI [1.55; 403.99] (p=0.02) * *In favour of long backboard*	1, 30 vs 30	Mahshidfar 2013

Mean ± SD (unless otherwise indicated)
* Calculations done by reviewer using Review Manager software
£ No SD's available, effect size and CI cannot be calculated
¥ Imprecision (large variability of results)
† Imprecision (lack of data)
§ Imprecision (limited sample size or low number of events)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Chan, 1996	Unclear, not specified in the article	Yes	No	No	Cross-over study
Cross, 2001	Unclear, not specified in the article	Yes, participants are doing both interventions and make a self-evaluation	No	No	Cross-over study
Hamilton, 1996	Unclear, not specified in the article	Yes, participants are doing both interventions and make a self-evaluation	No	No	Cross-over study
Johnson, 1996	Unclear, not specified in the article	Yes	No	No	Cross-over study
Lovell, 1994	Yes, no randomization	Yes	No	No	Within subjects; the thoracic sensor is not touching the

					surface on the backboard, no interface pressure can be measured
Luscombe 2003	Yes, no randomization	Yes	No	No	Within subjects
Mahshidfar, 2013	No	Yes, but irrelevant	no	no	
Sheerin 2007	Yes, no randomization	Yes	No	No	Within subjects,
Totten 1999	Unclear, not specified in the article	Yes	No	No	Cross-over study

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes/lack of data
Inconsistency	0	
Indirectness	-1	Most studies with healthy individuals
Publication bias	0	
QUALITY (GRADE)	**Final grading Very Low [D]**	

Conclusion	**Pain - comfort:** There is conflicting evidence from 8 experimental studies. It was shown that the long backboard resulted in a statistically significant increase of comfort in trauma patients with possible spinal injury, compared to the vacuum mattress splint (Mahshidfar 2013). However, in studies with healthy volunteers, it was shown that the long backboard resulted in a statistically significant increase of pain/discomfort, compared to the vacuum matress (Chan 1996, Cross 2001, Johnson 1996, Hamilton 1996, Keller 2005, Luscombe 2003, Totten 1999). Evidence is of very low quality and results cannot be considered precise due to limited sample size. **Interface pressure:** There is limited evidence from 3 experimental studies in favour of the vacuum mattress. In making this evidence conclusion, we place a higher value on statistical outcomes over non-statistical outcomes. It was shown that the vacuum mattress resulted in a statistically significant decrease of sacral, scapulae, heels, occipital interface pressure, compared to the backboard (Lovell 1994, Keller 2005, Sheerin 2007). A statistically significant decrease of sacral interface pressure, using the vacuum mattress compared to the backboard or padded backboard, could not be demonstrated (Keller 2005, Sheerin 2007). Evidence is of very low quality and results cannot be considered precise due to limited sample size, lack of data and/or large variability of results. **Immobilisation:** There is conflicting evidence from 4 experimental studies It was shown that the vacuum mattress resulted in a statistically significant increase of immobilisation in healthy volunteers, compared to the long spinal board (Johnson 1996, Hamilton 1996, Luscombe 2003). However, in studies with trauma patients with possible spinal injury, it was shown that the vacuum mattress resulted in a statistically significant decrease of immobilisation, compared to the long spinal board (Mahshidfar 2013). Evidence is of very low quality and results cannot be considered precise due to limited sample size.

Reference(s)	**Articles** Chan D, Goldberg RM, Mason J, Chan L. *Backboard versus mattress splint immobilization: a comparison of symptoms generated*. J Emerg Med. 1996, 14(3):293-298 Cross DA, Baskerville J. *Comparison of perceived pain with different immobilization techniques.* Prehosp Emerg Care. 2001, 5(3):270-274 Hamilton RS and Pons PT. *The efficacy and comfort of full-body vacuum splints for cervical-spine immobilization*. J Emerg Med 1996, 14(5):553-559 Johnson DR, Hauswald M, Stockhoff C. *Comparison of a vacuum splint device to a rigid backboard for spinal immobilization.* Am J Emerg Med. 1996, 14(4):369-372 Keller BP, Lubbert PH, Keller E, Leenen LP. *Tissue-interface pressures on three different support-surfaces for trauma patients.* Injury. 2005, 36(8):946-948 Lovell ME, Evans JH. *A comparison of the spinal board and the vacuum stretcher, spinal stability and interface pressure*. Injury. 1994, 25(3):179-180 Luscombe MD, Williams JL. *Comparison of a long spinal board and vacuum mattress for spinal immobilisation*. Emerg Med J. 2003, 20(5):476-478 Main PW, Lovell ME. *A review of seven support surfaces with emphasis on their protection of the spinally injured*. J Accid Emerg Med. 1996, 13(1):34-37 Mahshidfar B, Mofidi M, Yari A, Mehrsorosh S. *Long backboard versus vacuum mattress splint to immobilize whole spine in trauma victims in the field: a randomized clinical trial*. Prehospital and Disaster Medicine 2013, 28(5):462-465 Sheerin F, de Frein R. *The occipital and sacral pressures experienced by healthy volunteers under spinal immobilization: a trial of three surfaces*. J Emerg Nurs. 2007, 33(5):447-450 Totten V, Sugarman D. *Respiratory effects of spinal immobilization*. Prehosp Emerg Care. 1999, 3(4):347-352 **Systematic reviews** Ahmad M, Butler J. *BestBET: Spinal boards or vacuum mattresses for immobilisation.* BestBET 2007 Ahn H, Singh J, Nathens A, MacDonald RD, Travers A, Tallon J, Fehlings MG, Yee A. *Pre-hospital care management of a potential spinal cord injured patient: a systematic review of the literature and evidence-based guidelines.* J Neurotrauma. 2011, 28(8):1341-1361. Kwan I, Bunn F, Roberts IG. *Spinal immobilization for trauma patients*. Cochrane review 2009

Spine injury – Vacuum mattress (Feasibility)

Question (PICO)	In humans with a spinal injury (P), is application of a vacuum mattress by laypeople (I) compared to application of a vacuum mattress by professional first responders (C) less effective to change survival, functional recovery, pain, complications, time to resolution of symptoms (O)?
Search Strategy	Databases **GIN, NGC** (guidelines) using the search terms 'spine injury' OR 'cervical injury' OR 'backboard' OR 'spine board' OR 'vacuum mattress' **BestBET** (best evidence topics) using the search terms: 'spine' OR 'cervical' OR 'board' **The Cochrane Library** (systematic reviews) using the following search term: MeSH descriptor: [spinal injury] explode all trees **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Spinal injury"] OR ((cercival:ti,ab,kw OR spinal:ti,ab,kw) AND injur*:ti,ab,kw) 2. "backboard":ti,ab,kw OR "mattress":ti,ab,kw OR 'spine board':ti,ab,kw OR "vacuum":ti,ab,kw OR "log roll":ti,ab,kw OR [mh "Patient Transfer"] 3. #1 and #2

	MEDLINE (via PubMed interface) using the following search strategy: 1. "Cervical Vertebrae/injuries"[Mesh] OR "Spinal Cord Injuries"[Mesh] OR ((cervical[TIAB] OR spinal[TIAB]) AND injur*[TIAB]) 2. backboard [TIAB] OR "spine board"[TIAB] OR vacuum [TIAB] OR padded [TIAB] OR mattress [TIAB] OR "Immobilization" [Mesh] OR "Transportation of Patients"[Mesh] OR "log roll"[TIAB] OR "patient transport"[TIAB] OR "6-plus-person"[TIAB] OR 6PP[TIAB] 3. 1 AND 2 **Embase** (via Embase.com interface) using the following search strategy: 1. 'spinal cord injury'/exp OR 'cervical spine'/exp OR ((cervical:ab,ti OR spinal:ab,ti) AND injur*:ab,ti) 2. 'fracture immobilization'/exp OR 'backboard':ab,ti OR 'spine board':ab,ti OR 'vacuum':ab,ti OR 'mattress':ab,ti OR 'stretcher':ab,ti OR 'padded':ab,ti OR 'splint':ab,ti OR ('patient transport'/exp OR 'patient transport':ab,ti OR 'log roll':ab,ti OR '6-plus-person':ab,ti) 3. 1 AND 2 Selected articles were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	02 July 2015
In/Exclusion criteria	**Population**: We included studies with healthy volunteers or trauma victims. **Intervention**: Include: vacuum mattress applied by lay people Exclude: devices which are only used in emergency departments (such as special types of mattresses). **Comparison**: Include: vacuum mattress applied by professional first aid responders **Outcome**: Include: studies measuring time and ease of application Exclude: studies measuring physical outcomes **Study design** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year:** Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No relevant studies were identified using the above search strategy and criteria.
Reference(s)	/

Cervical spine injury – Immobilisation with head blocks (First Aid)

Question (PICO)	In humans with a cervical spine injury (P), is immobilisation with headblocks (I) compared to no immobilisation (C) effective to change survival, functional recovery, pain, complications, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Spinal injury"] OR ((cercival:ti,ab,kw OR spinal:ti,ab,kw) AND injur*:ti,ab,kw) 2. head block*:ti,ab,kw OR head immobil*:ti,ab,kw 3. #1 and #2 **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "Cervical Vertebrae/injuries"[Mesh] OR ((cervical[TIAB] OR spinal[TIAB]) AND injur*[TIAB]) 2. head block*[TIAB] OR head immobil*[TIAB] 3. 1 AND 2 **Embase** (via Embase.com interface) using the following search strategy: 1. 'cervical spine'/exp OR ((cervical:ab,ti OR spinal:ab,ti) AND injur*:ab,ti) 2. head block*:ab,ti OR head immobil*:ab,ti 3. 1 AND 2 Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	15 July 2015
In/Exclusion criteria	**Population** Include: People with cervical spine injury or healthy volunteers **Intervention** Include: the use of head blocks for the immobilization of the head. **Comparison** Include: no use of head blocks, no immobilization of the head. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Holla, 2012, The Netherlands	Experimental: non-randomised controlled trial	10 healthy subjects (6 male, 4 female), age 23-47 years were	1. Rigid collar: Select Stifneck collar	

	(within subjects design)	selected to test the rigid collar, the head blocks strapped on the backboard and a combination of both.	2. Sof-Loc head blocks: two vinyl-dipped foam blocks strapped with two Velcro straps on both sides of the head to a padded spine board 3. No immobilization [data on rigid collar were not extracted]	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Lateral flexion (°)	Head blocks vs no immobilisation	Statistically significant: 10±10 vs 77±15 MD: -67 (p<0.005) £ *In favour of head blocks*	1, 10 vs 10 § (within subjects design)	Holla, 2012
Flexion-extension (°)		Statistically significant: 6±6 vs 114±5 MD: -108 (p<0.005) £ *In favour of head blocks*		
Rotation (°)		Statistically significant: 8±5 vs 151±25 MD: -143 (p<0.005) £ *In favour of head blocks*		

Mean ± SD

£ No SD's available, effect size and CI cannot be calculated [only if applicable for more than one cell]

§ Imprecision (limited sample size)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Holla, 2012	No	No	No	No	

Level of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Limited sample sizes
Inconsistency	0	
Indirectness	-1	Study performed on healthy volunteers
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [C]**	

Conclusion	There is limited evidence in favour of using head blocks for immobilisation. It was shown that the use of head blocks resulted in a statistically significant decrease of lateral flexion, flexion-extension and rotation, compared to no head blocks (Holla 2012). Evidence is of very low quality and results cannot be considered precise due to limited sample size and lack of data.
Reference(s)	**Articles** Holla M. *Value of a rigid collar in addition to head blocks: a proof of principle study*. Emerg Med J 2012, 29:104-107

Help! Eerste hulp voor iedereen

-

Help! Eerste hulp voor hulpverleners

Bijlagen

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Inhoudsopgave

Bijlage 1: ES Skin wounds – Disinfectant solution

Question (PICO)	In humans with a simple skin wound (P), is cleansing the wound with a disinfectant solution (I) compared to cleansing with (saline/tap) water or no cleansing with a disinfectant solution (C) effective to change tissue healing, functional recovery, pain, complications, time to resumption of usual activities, restoration to the pre-exposure condition, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "wound, penetrating"] OR [mh "lacerations"] OR [mh "wounds,nonpenetrating"] OR laceration*:ti,ab,kw OR cut:ti,ab,kw OR cuts:ti,ab,kw OR graze*:ti,ab,kw OR "wound":ti,ab,kw OR "wounds":ti,ab,kw OR "nonpenetrating wound":ti,ab,kw OR "nonpenetrating wounds":ti,ab,kw OR "penetrating wound":ti,ab,kw OR "penetrating wounds":ti,ab,kw 2. [mh "merbromin"] OR [mh "povidone-iodine"] OR [mh "saline solution,hypertonic"] OR [mh "ether"] OR Mercurochrome:ti,ab,kw OR Merbromine:ti,ab,kw OR ether:ti,ab,kw OR "povidone iodine":ti,ab,kw OR "povidone-iodine":ti,ab,kw OR "saline":ti,ab,kw OR [mh "chlorine"] OR "chlorine":ti,ab,kw OR [mh "chlorhexidine"] OR "chlorhexidine":ti,ab,kw OR [mh "cetrimonium compounds"] OR "cetrimides":ti,ab,kw 3. cleans*:ti,ab,kw OR irrigat*:ti,ab,kw 4. 1-3 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "lacerations"[Mesh] OR wounds, penetrating[Mesh] OR "wounds,nonpenetrating"[Mesh] OR laceration*[TIAB] OR cut[TIAB] OR cuts[TIAB] OR graze*[TIAB] OR wound[TIAB] OR wounds[TIAB] OR "nonpenetrating wound"[TIAB] OR "nonpenetrating wounds"[TIAB] OR "penetrating wound"[TIAB] OR "penetrating wounds"[TIAB] 2. Merbromin[Mesh] OR "povidone-iodine"[Mesh] OR "saline solution,hypertonic"[Mesh] OR ether[Mesh] OR Mercurochrome[TIAB] OR Merbromine[TIAB] OR ether[TIAB] OR "povidone iodine"[TIAB] OR "povidone-iodine"[TIAB] OR "saline"[TIAB] OR "Chlorine"[Mesh] OR chlorine[TIAB] or chlorhexidine[Mesh] OR chlorhexidine[TIAB] OR "cetrimonium compounds"[Mesh] OR "cetrimides"[TIAB] 3. cleans*[TIAB] OR irrigat*[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. laceration/exp OR 'penetrating trauma'/exp OR blunt trauma/exp OR wound/exp OR laceration*:ab,ti OR cut:ab,ti OR cuts:ab,ti OR graze*:ab,ti OR 'skin wound':ab,ti OR 'skin wounds':ab,ti OR 'nonpenetrating wound':ab,ti OR 'nonpenetrating wounds':ab,ti OR 'penetrating wound':ab,ti OR 'penetrating wounds':ab,ti 2. merbromin/exp OR povidone iodine/exp OR sodium chloride/exp OR ether/exp OR merbromine:ab,ti OR ether:ab,ti OR 'povidone iodine':ab,ti OR 'povidone-iodine':ab,ti OR 'saline':ab,ti OR chlorine/exp OR chlorine:ab,ti OR chlorhexidine/exp OR chlorhexidine:ab,ti OR cetrimide/exp OR cetrimide:ab,ti 3. cleans*:ab,ti OR irrigat*:ab,ti 4. 1-3 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	05/08/2015
In/Exclusion criteria	**Population:** Include: sick or injured people or healthy volunteers of all ages. Trials involving people of all ages with a wound (prior to suturing). A wound is defined as a break in the skin. **Intervention:** Include: disinfectant solutions that can be provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers) including a solution containing povidone-iodine, mercurochrome, ether, chlorine, chlorhexidine, cetrimide

	Comparison: Include: saline solution (salt water solution), tap water or no intervention. Exclude: any other disinfectant solution **Outcome**: Include: wound infection, proportion of wounds that healed, rate of wound healing, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomized controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Fournel, 2010, France	Systematic review	24 randomized controlled trials including 5004 patients undergoing surgery: 2465 patients receiving intra-operative povidone-iodine application (intervention) and 2539 patients receiving no antiseptic solution (control)	Intervention: intra-operative povidone-iodine application (i.e. povidone-iodine just before or after wound closure) Control: no antiseptic solution (saline or nothing)	From the 24 RCT's, 15 were considered as high-quality and were selected for data-extraction

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Surgical site infection	Povidone-iodine solution vs Saline/no solution	Statistically significant: 128/1605 vs 224/1676 RR: 0.58, 95%CI [0.40;0.83] (p=0.003) *In favour of povidone-iodine solution*	15, 1605 vs 1676	Fournel, 2010

Quality of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See systematic review Fornel 2010 (table 2)
Imprecision	0	
Inconsistency	0	
Indirectness	-1	Hospital setting, surgical wounds
Publication bias	0	
QUALITY (GRADE)	**Final grading Moderate [B]**	

Conclusion	There is evidence in favour of povidone-iodine solution . It was shown that a povidone-iodine solution resulted in a statistically significant decreased risk of surgical-site infection, compared to saline/no solution (Fornel 2010). Evidence is of moderate quality.
Reference(s)	**Systematic reviews** Fournel I, Tiv M, Soulias M, Hua C, Astruc K, Aho Glélé LS. *Meta-analysis of intraoperative povidone-iodine application to prevent surgical-site infection.* Br J Surg 2010, 97:1603-1613.

Bijlage 2: Spine injury – Chin lift vs jaw thrust

Question (PICO)	Among persons with a spine injury (P), does opening the airway by chin lift (I) compared to doing the jaw thrust (C) change survival, functional recovery, pain, complications, time to resolution of symptoms (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the search terms: 1. [mh "**Spinal injury**"] OR (spine NEXT injur*):ti,ab,kw OR (spinal NEXT injur*):ti,ab,kw OR (cervical NEXT injur*):ti,ab,kw OR (cervical NEXT spine*):ti,ab,kw OR 'cervical vertebrae':ti,ab,kw 2. (jaw NEXT thrust*):ti,ab,kw OR 'chin lift':ti,ab,kw OR 'neck lift':ti,ab,kw 3. 1 AND 2 **MEDLINE** (via PubMed interface) for guidelines, systematic reviews or experimental studies using the following search strategy: 1. "Cervical Vertebrae/injuries"[Mesh] OR cervical injur*[TIAB] OR cervical spine*[TIAB] OR "Spinal Cord Injuries"[Mesh] OR spinal injur* [TIAB] OR spine injur* [TIAB] 2. jaw thrust*[TIAB] OR "chin lift"[TIAB] OR "neck lift"[TIAB] OR "neck tilt"[TIAB] OR "chin tilt"[TIAB] 3. 1 AND 2 **Embase** (via Embase.com interface) for systematic reviews or experimental studies using the following search strategy: 1. 'spinal cord injury'/exp OR 'cervical spine'/exp OR (cervical NEXT/1 injur*):ab:ti OR (cervical NEXT/1 spin*):ab:ti OR 'spine injury'/exp OR (spinal NEXT/1 injur*):ab:ti OR (spine NEXT/1 injur*):ab:ti 2. (jaw NEXT/1 thrust*):ab:ti OR 'Chin lift':ab:ti OR 'Neck lift':ab:ti OR 'neck tilt':ab:ti OR 'chin tilt':ab:ti 3. 1 AND 2 Selected articles were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	09-03-2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages; cadavers **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies. **Language**: Include: English **Publication year**: Include: all years

Characteristics of included studies

Author, Year, Country	Study design	Population	Comparison	Remarks
Prasarn, 2014, USA	Experimental: Non-randomised controlled trial (within subject design)	9 human cadavers with unstable, dissociative C1–C2 injuries (surgically created)	jaw thrust vs chin lift	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Angular motion occurring at C1–C2 (degrees): Flexion/extension	chin lift vs jaw thrust	Statistically significant: 12.1 vs 4.3 MD: 7.8 (p<0.001) *in favour of jaw thrust* No SD or CI reported. †	1, 9 vs 9 § (within subject design)	Prasarn 2014
Angular motion occurring at C1–C2 (degrees): Rotation		Statistically significant: 4.1 vs 2.3 MD: 1.8 (p=0.013) *in favour of jaw thrust* No SD or CI reported. †		
Angular motion occurring at C1–C2 (degrees): Lateral flexion		Statistically significant: 5.9 vs 2.2 MD: 3.7 (p=0.002) *in favour of jaw thrust* No SD or CI reported. †		
Translation motion occurring at C1–C2 (mm): Flexion/extension		Not statistically significant: 5.5 vs 3.3 MD: 2.2 (p=0.056) No SD or CI reported. †		
Translation motion occurring at C1–C2 (mm): Rotation		Statistically significant: 8.1 vs 2.5 MD: 5.6 (p=0.003) *in favour of jaw thrust* No SD or CI reported. †		
Translation motion occurring at C1–C2 (mm): Lateral flexion		Statistically significant: 9.7 vs 5.9 MD: 3.8 (p=0.003) *in favour of jaw thrust* No SD or CI reported. †		

¥ Imprecision (large variability of results)

† Imprecision (lack of data)

§ Imprecision (limited sample size)

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Prasarn 2014	No	Yes – but shouldn't influence outcome	No	No	Use of cadavers

	Initial grading High [A]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	-1	Small number of participants and lack of data
Inconsistency	0	
Indirectness	-1	Use of cadavers
Publication bias	0	
QUALITY (GRADE)	**Final grading Very Low [D]**	

Conclusion(s)	There is limited evidence in favour of the jaw thrust to improve airway patency in the trauma patient with suspected cervical spine injury. It was shown that jaw thrust resulted in a statistically significant decrease of the angular motion (flexion/extension; rotation; lateral bending) and translational motion (rotation; lateral bending) compared to chin lift (Prasarn 2014). A statistically significant decrease of translational motion (flexion/extension), using jaw thrust compared to chin lift could not be demonstrated (Prasarn 2014). Evidence is of very low quality and results of these studies are imprecise due to small number of participants and lack of data.
Reference(s)	**Articles** Prasarn ML, Horodyski M, Scott NE, Konopka G, Conrad B, Rechtine GR. *Motion generated in the unstable upper cervical spine during head tilt-chin lift and jaw thrust maneuvers.* Spine J. 2014, 14(4):609-614

Bijlage 3: ES Muscle cramps – Heat application

Question (PICO)	In humans (P), is heat application (I) effective as treatment of exercise-associated muscle cramps (O) compared to no heat application (C)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh immersion] OR [mh hot temperature] OR immersion:ti,ab,kw OR 'hot':ti,ab,kw OR 'heat':ti,ab,kw OR 'warm':ti,ab,kw 2. [mh "muscle cramp"] OR [mh "musculoskeletal pain"] OR [mh "athletic injuries"] OR cramp:ti,ab,kw OR cramps:ti,ab,kw OR "delayed onset muscle soreness":ti,ab,kw OR "delayed onset muscular soreness":ti,ab,kw 3. 1 AND 2 **MEDLINE** (via PubMed interface) using the following search strategy: 1. "immersion"[Mesh] OR immersion*[TIAB] OR "hot temperature"[Mesh] OR "hot"[TIAB] OR "warm"[TIAB] OR "heat"[TIAB] 2. "muscle cramp"[Mesh] OR "musculoskeletal pain"[mesh] OR "athletic injuries"[Mesh] OR "cramp"[TIAB] OR "cramps"[TIAB] OR "delayed onset muscle soreness"[TIAB] OR "delayed onset muscular soreness"[TIAB] 3. 1 AND 2 **Embase** (via Embase.com interface) using the following search strategy: 1. 'immersion'/exp OR immersion*:ab,ti OR 'heat'/exp OR 'hot':ab,ti OR 'warm':ab,ti OR 'heat':ab,ti 2. 'muscle cramp'/exp OR 'musculoskeletal pain'/exp OR 'sport injury'/exp OR cramp:ab,ti OR cramps:ab,ti OR 'delayed onset muscle soreness':ab,ti OR 'delayed onset muscular soreness':ab,ti 3. 1 AND 2
Search date	20-02-2015
In/Exclusion criteria	**Population**: Include: healthy volunteers of all ages. **Intervention**: Include: heat application that can be provided by lay people. Exclude: heat application that cannot provided by lay people, heat application applied in a non-acute setting (≥24 hours after exercise) **Comparison**: Include: no intervention **Outcome**: Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: blood biomarkers **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies.

Characteristics of included studies

Author, year, Country	Study design	Population	Risk factor	Remarks
Petrofsky, 2012, USA	Experimental: randomized controlled trial	20 healthy individuals between the ages of 20 and 40 years, BMI<40. Subjects had no cardiovascular or hepatic disease, no diabetes, upper limb neuropathy or recent upper limb	Intervention: continuous, low-level heat wrap (ThermaCare® heat wraps, OH, USA) applied immediately after the exercise and left in place for 8 h.	All subjects exercised in four sets. Each set involved 25 bicep curls against resistance until fatigue. The resistance was 35% of

		injuries, and were not diagnosed with rhabdomyolysis, since this disease causes the release of MB and cytokines even without exercise.	Control: no intervention	their maximum strength.
Petrofsky, 2015, USA	Experimental: randomized controlled trial	One hundred healthy subjects (20-30 years) at similar fitness levels were examined. All subjects did not participate in regular sports activities and were students at Loma Linda University. They had no training in squats or involving squats. Subjects were almost equally divided between men and women and the portion of men and women was the same in each group of subjects. All subjects were nonsmokers. Subjects had no cardiovascular disease, hepatic disease, diabetes, lower limb neuropathies, or recent lower limb injuries.	Intervention: application of ThermaCare heat wrap immediately after exercise for 8 hours (on each leg centered over the quadriceps and lying longitudinally over the muscle) Control: no intervention	All subjects accomplished leg squats for 3*5 minutes

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Self-reported soreness (Visual Analogue Scale, 0-10) (3 hours post-exercise)	Heat wrap vs no intervention	Statistically significant: 2.0±0.35 vs 5.8±0.4 λ MD: -3.8, 95%CI [-3.45;-1.95] (p<0.00001) * *in favour of heat application*	1, 5 vs 5 §	Petrofsky, 2012
Self-reported soreness (Visual Analogue Scale, 0-10) (24 hours post-exercise)		Statistically significant: 4.2±0.7 vs 6.9±0.5 λ MD: -2.7, 95%CI [-4.27;-3.33] (p<0.00001) * *in favour of heat application*		
		Statistically significant: 3.2±0.3 vs 5.3±0.8 λ MD: -2.1, 95%CI [-2.47;-1.73] (p<0.00001) * *in favour of heat application*	1, 20 vs 20 §	Petrofsky, 2015
Self-reported soreness (Visual Analogue Scale, 0-10) (48 hours post-exercise)		Statistically significant: 3.2±0.7 vs 6.7±0.5 λ MD: -3.5, 95%CI [-4.25;-2.75] (p<0.00001) * *in favour of heat application*	1, 5 vs 5 §	Petrofsky, 2012
		Statistically significant: 3.8±0.6 vs 5.5±1.0 λ MD: -1.7, 95%CI	1, 20 vs 20 §	Petrofsky, 2015

		[-2.14;-1.26] (p<0.00001) * *in favour of heat application*		
Self-reported soreness (Visual Analogue Scale, 0-10) (72 hours post-exercise)		Statistically significant: 1.9±0.4 vs 3.4±0.7 λ MD: -1.5, 95%CI [-2.21;-0.79] (p<0.0001) * *in favour of heat application*	1, 5 vs 5 §	Petrofsky, 2012
		Statistically significant: 2.0±0.3 vs 3.0±0.6 λ MD: -1.0, 95%CI [-1.29;-0.71] (p<0.0001) * *in favour of heat application*	1, 20 vs 20 §	Petrofsky, 2015

Mean ± SD (unless otherwise indicated)
* Calculations done by the reviewer(s) using Review Manager software
§ Imprecision (limited sample size)
λ Data extracted from graph

Quality of evidence

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
Petrofsky, 2012	Unclear	No	No	No	
Petrofsky, 2012	Unclear	Unclear	No	No	

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Limited sample size
Inconsistency	0	
Indirectness	-1	Soreness as indirect outcome for muscle cramps
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is limited evidence in favour of heat application. It was shown that the application of heat wraps immediately after exercise resulted in a statistically significant decreased muscle soreness (from 3 hours to 72 hours after exercise), compared to no intervention (Petrofsky 2012, Petrofsky 2015). Evidence is of low quality and results cannot be considered precise due to limited sample size.
Reference(s)	**Individual studies** Petrofsky J., Laymon M, Berk L, Al-Nakhli HH, Banh A, Eisentrout A, Tokar A, Valentine M, Batt J. *Pilot study: Physiological evidence that heat reduces pain and muscle damage in delayed-onset muscle soreness*. Clinical Practice 2012, 9(6):639-650. Petrofsky J, Khowailed IA, Lee H, Berk L, Bains G, Akerkar S, Shah J, Al-Dabbak F, Laymon M. *COLD VRS HEAT AFTER EXERCISE- IS THERE A CLEAR WINNER FOR MUSCLE SORENESS*. J Strength Cond Res. 2015.

Bijlage 4: ES Mosquito Sting – Electronic mosquito repellents

Question (PICO)	Among adults and children (P), does the use of electronic mosquito repellent (I) compared to not using this (C) prevent mosquito stings (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: [mh "Culicidae"] AND [mh "Primary Prevention"] **MEDLINE** (via PubMed interface) for existing systematic reviews, using the following search strategy: 1. "Culicidae"[Mesh] OR mosquito*[TIAB] OR Culicidae [TIAB] OR Culex [TIAB] 2. ((Electronic[TIAB] OR ultrasound[TIAB] OR ultrasonic[TIAB]) AND (repel*[TIAB] OR control[TIAB])) OR EMR[TIAB] 3. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 1. Mosquito/exp OR Culex/exp OR mosquito*:ab,ti OR culicidae:ab,ti OR culex:ab,ti 2. ((electronic:ab,ti OR ultrasound:ab,ti OR ultrasonic:ab,ti) AND (repel*:ab,ti OR control*:ab,ti)) OR EMR:ab,ti 3. 1-2 AND systematic reviews, retrieved with the above searches, and used as source for individual studies: Enayati, 2010
Search date	9-07-2015
In/Exclusion criteria	**Population**: Include: adults or children **Intervention**: Include: electronic mosquito repellents **Comparison:** Include: dummy EMRs, inoperable EMRs, EMRs switched off or no EMRs. Exclude: other repellents and treated or untreated bed nets as control. **Outcome**: Include: number of mosquitos landing on exposed body parts of humans acting as baits. Malaria infection. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Enayati, 2012, Iran	Systematic Review	10 studies containing 22 experiments of which 7 experiments were excluded because they were laboratory based or used chemical repellents. The 15 included experiments were field experiments.	EMR vs no EMR EMRs had a frequency between 125 Hz and 75,600 Hz.	This systematic review was considered as stable in 2012. No further updates will be performed.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Mean landing rate	EMR switched on vs EMR switched off	Not statistically significant: 2-7 landings/min	1, 12 observers, 12 observations §	Enayati, 2012

		no significant difference between groups p>0.01 £†		
		Not statistically significant: 240 vs 193 p>0.05 £†	1, 6 observers, 30 observations §	
		Not statistically significant: 14.5 vs 13.2 p>0.05 £†	2, 2 observers, 10 observations §	
		Not statistically significant: 500 vs 497 p>0.05 £†	1, 3 observers, 15 observations §	
	EMR vs no EMR	Not statistically significant: 146.5 v 68.78 p>0.05 £†	1, 1 observer, 7 observations §	
		Not statistically significant: 561.5 vs 538 p>0.05 £†	1, 3 observers, 12 observations §	
		Not statistically significant: 806 vs 720 p>0.05 £†	3, 5 observers, 28 observations §	
	ME electronic mosquito repellent vs no EMR	Not statistically significant: 8.9 vs 8.4 p>0.05 £†	1, 5 observers, 12 observations §	
	Buzz-off repellent vs no EMR	Not statistically significant: 16.8 vs 14.9 p>0.05 £†		
		Not statistically significant: 25 vs 30 p>0.05 £†	1, 4 observers, 44 observations §	
	Norris Electronic Mosquito repeller vs no EMR	Not statistically significant: 36 vs 30 p>0.05 £†		
	Functional EMR vs inoperable EMR	Not statistically significant: 23.4 vs 22.7 p>0.05 £†	1, 18 observers, 324 observations	

£ No SD's available, effect size and CI cannot be calculated
† Imprecision (lack of data)
§ Imprecision (limited sample size or low number of events)

Quality of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See table Systematic Review Enayati
Imprecision	-1	Limited sample sizes/lack of data
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Moderate [B]**	

Conclusion(s)	There is limited evidence neither in favour of the intervention nor the control. A statistically significant decrease of mosquito landings, using EMR compared to no EMR or inoperable EMR, could not be demonstrated (Enayati 2012). Evidence is of moderate quality and results of these studies are imprecise due to limited sample size and/or lack of data.
Reference(s)	**Systematic reviews** Enayati A, Hemingway J, Garner P. *Electronic mosquito repellents for preventing mosquito bites and malaria infection*. Cochrane Database of Systematic Reviews 2012, Issue 4. Art. No.: CD005434

Bijlage 5: ES Frostbite – Special clothing

Question (PICO)	In humans (P), is wearing special clothing (I) compared to not wearing special clothing (C) a protective factor for frostbite (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh "Frostbite"] OR frostbite:ti,ab 2. [mh Clothing] OR cloth*:ti,ab 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 4. "Frostbite"[Mesh] OR frostbite[TIAB] 5. "Clothing"[Mesh] OR clothing[TIAB] 6. 1-2 AND **Embase** (via Embase.com interface) using the following search strategy: 7. 'frostbite'/exp OR frostbite:ab,ti 8. 'clothing'/exp OR cloth*:ab,ti 9. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	16 September 2015
In/Exclusion criteria	**Population:** Include: adults or children **Intervention:** Include: wearing protective/special clothing **Comparison:** Include: not doing this **Outcome:** Include: risk of frostbite **Study design:** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting only means, but no SDs, effect sizes, p-values. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies

Author, year, Country	Study design	Population	Risk factor	Remarks
Lehmuskalio, 1995, Finland	Observational: case-control study	Cases: 913 young male conscripts with local frostbite of the head that needed medical attention Controls: 2478 uninjured control conscripts (two conscripts who had not developed frostbite were randomly selected from the same squads as the injured soldiers to act as controls)	Multiple risk factors [only data on risk factors concerning clothing were extracted]	

Synthesis of findings

Outcome	Risk factor	Effect Size	#studies, # participants	Reference
Risk of frostbite (ears)	Not wearing a hat with ear flaps	Statistically significant: OR: 18.5, 95%CI [14.0606;24.3411] * (p<0.0001) *With harm for not wearing a hat with ear flaps*	1, 913 vs 2478	Lehmuskalio, 1995
Risk of frostbite (ears)	Not wearing scarf	Statistically significant: OR: 2.1, 95%CI [1.5961;2.7630] * (p<0.0001) *With harm for not wearing a scarf*		
Risk of frostbite (other part of face)		Statistically significant: OR: 3.8, 95%CI [2.6703;5.4075] * (p<0.0001) *With harm for not wearing a scarf*		

* 95%CI calculated from SE using Review Manager software

Quality of evidence

Author, Year	Inappropiate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations
Lehmuskalio, 1995	No	No	No (multivariate analysis)	No	

Level of the body of evidence

	Initial grading Low [C]	Downgrading due to
Limitations of study design	0	
Imprecision	0	
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	There is limited evidence in favour of wearing a hat with earflaps and wearing a scarf. It was shown that wearing a hat with earflaps and wearing a scarf resulted in a statistically significant decreased risk of frostbite compared to not doing this (Lehmuskalio 1995). Evidence is of low quality.
Reference(s)	Lehmuskallio E, Lindholm H, Koskenvuo K, Sarna S, Friberg O, Viljanen A. *Frostbite of the face and ears: epidemiological study of risk factors in Finnish conscripts*. BMJ 1995, 311(7021):1661-3

Bijlage 6: ES Hypothermia – Moving

Question (PICO)	In humans with hypothermia (P), is moving the victim (I) compared to not moving the victim (C) a risk factor for harm to the vital functions (O)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. [mh hypothermia] OR hypothermia:ti,ab,kw 2. [mh movement] OR mov* OR evacuat*:ti,ab,kw OR emergency remov*:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 10. "Hypothermia" [Mesh] OR "hypothermia" [TIAB] 11. movement[Mesh] OR mov*[TIAB] OR evacuat*[TIAB] OR emergency remov*[TIAB] 12. "risk factors"[Mesh] OR risk*[TIAB] 13. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'hypothermia'/exp OR 'hypothermia':ab,ti 2. 'movement (physiology)'/exp OR mov* OR evacuat*:ab,ti OR (emergency NEXT\1 remov*):ab,ti 3. 'risk factor'/exp OR risk*:ab,ti 4. 1-2 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	16 July 2015
In/Exclusion criteria	**Population:** Include: people with hypothermia. **Intervention:** Include: moving of people with hypothermia. **Comparison:** Include: not moving people with hypothermia. **Outcome:** Include: survival, functional recovery, pain, complications, time to resumption of usual activity, restoration to the pre-exposure condition, time to resolution of symptoms or other health outcome measures (including adverse effects). Exclude: measures of performance by basic first responders or lay caregivers and/or community health workers. **Study design:** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies. **Language**: Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline) **Publication year**: Include: all years

Characteristics of included studies
Not applicable

Synthesis of findings
Not applicable

Quality of evidence
Not applicable

Conclusion	No evidence was found with the above search strategy and criteria.
Reference(s)	Not applicable

Bijlage 7: ES Pregnancy and delivery – Breast feeding (child outcomes)

Question (PICO)	In newborn babies (P), is early breastfeeding (I) compared to later breastfeeding (C) effective for health-related outcomes (O)?
Search Strategy	Databases **The Cochrane Library** using the following search strategy: 1. [mh "breast feeding"] OR "breastfeeding":ti,ab,kw OR "breast feeding":ti,ab,kw OR suckl*:ti,ab,kw 2. Early:ti,ab,kw OR delayed:ti,ab,kw 3. [mh "infant, newborn"] OR newborn*:ti,ab,kw OR neonat*:ti,ab,kw 4. 1-3 AND **MEDLINE** (via PubMed interface) for guidelines and systematic reviews using the following search strategy: 1. "Breast feeding"[Mesh] OR "breastfeeding"[TIAB] OR "breast feeding"[TIAB] OR suckl*[TIAB] 2. early[TIAB] OR delayed[TIAB] 3. "Infant, newborn"[Mesh] OR newborn*[TIAB] OR neonat*[TIAB] 4. ((((((((((Meta-Analysis as Topic[Mesh])) OR ((meta analy*[TIAB]))) OR ((metaanaly*[TIAB]))) OR ((Meta-Analysis[Publication Type]))) OR ((systematic review*[TIAB] OR systematic overview*[TIAB]))) OR ((Review Literature as Topic[Mesh])))) OR ((cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB]))) OR ((reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB]))) OR ((((selection criteria[TIAB] OR data extraction[TIAB])) AND ((Review[PT]))))) NOT ((Comment[PT] OR Letter[PT] OR Editorial[PT] OR animal[Mesh] NOT (animal[Mesh] AND human[Mesh]))) 5. 1-4 AND **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Breast feeding"[Mesh] OR "breastfeeding"[TIAB] OR "breast feeding"[TIAB] OR suckl*[TIAB] 2. early[TIAB] OR delayed[TIAB] 3. "perinatal mortality"[Mesh] OR "infant mortality"[Mesh] OR "child mortality"[Mesh] OR mortal*[TIAB] OR "body temperature"[Mesh] OR temperature[TIAB] OR hypothermia[Mesh] OR hypothermia[TIAB] OR hypoglycemia[Mesh] OR hypoglycemia[TIAB] OR hypoglycaemia[TIAB] 4. "Infant, newborn"[Mesh] OR newborn*[TIAB] OR neonat*[TIAB] 5. 1-4 AND **Embase** (via Embase.com interface) for guidelines and systematic reviews using the following search strategy: 1. 'Breast feeding'/exp OR 'breastfeeding':ab,ti OR 'breast feeding':ab,ti 2. Early:ab,ti OR late:ab,ti OR delayed:ab,ti 3. 'Newborn'/exp OR newborn*:ab,ti OR neonat*:ab,ti 4. 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti 5. 1-4 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'Breast feeding'/exp OR 'breastfeeding':ab,ti OR 'breast feeding':ab,ti 2. Early:ab,ti OR delayed:ab,ti 3. 'perinatal mortality'/exp OR 'infant mortality'/exp OR 'childhood mortality'/exp OR mortality:ab,ti OR 'body temperature'/exp OR temperature:ab,ti OR hypothermia/exp OR hypothermia:ab,ti OR hypoglycemia/exp OR hypoglycemia:ab,ti OR hypoglycaemia:ab,ti 4. 'Newborn'/exp OR newborn*:ab,ti OR neonat*:ab,ti 5. 1-4 AND

	Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	29/07/2015
In/Exclusion criteria	**Population:** Included: term infants, new-borns. Exclude: (very) low birth weight and pre-term infants. **Intervention:** Include: early breast feeding **Comparison:** Include: late/delayed breast feeding. Exclude: breastfeeding vs no breastfeeding. **Outcome:** Include: direct health-related outcomes related to the newborn child, i.e. neonatal mortality, body temperature, hypothermia, hypoglycemia,…. **Study design**: Include: a systematic review was included if the search strategy and selection criteria are clearly described and if at least MEDLINE and one other relevant database was searched. If no systematic review was published within the last 5 years, individual experimental and/or observational studies were included. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values. **Language:** Include: English (only for newly identified evidence); English, French, German, Dutch (for evidence included in the earlier version of the guideline)

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Edmond, 2006, Ghana	Observational: cohort study	10947 singleton infants born between July 1, 2003 and June 30, 2004 who initiated breast feeding, survived day 2 and whose mothers were visited in the neonatal period. Follow-up was every 4 weeks until they reached 12 months of age.	Early breastfeeding (< day 1) vs late breastfeeding (> 1 day)	
Edmond, 2007, Ghana	Observational: cohort study	10942 singleton infants born between July 1, 2003 and June 30, 2004 who initiated breast feeding, survived day 2 and whose mothers were visited in the neonatal period. Follow-up was every 4 weeks until they reached 12 months of age.	Early breastfeeding (< day 1) vs late breastfeeding (> 1 day)	Sample size and power were calculated: the 10000 infants included in this study provided 80% power to detect a 1.4 fold effect on neonatal mortality at a significance level of 5% and mortality risk of 2.9% in the breastfed group
Gunnlaugson, 1993, Guinea Bissau	Observational: cohort study	734 mothers are visited after vaginally delivering full term singleton new-borns by a health worker between 1984 and 1986 asking the day and hour when the child was first given	Early breastfeeding (<1 day) vs late breastfeeding (≥1 day)	postneonatal mortality: infants aged between 29 days to 3 years)

		the breast. 717 children were included in the study. Follow-up every 3 months for one to three years.		
van den Bosch, 1990, Malawi	Experimental: randomised controlled trial	160 women were included after spontaneous vertex delivery between 8 am and 1.30 pm. Babies were randomly assigned to an early suckling group (n=81) or a control group (n=79). Observations were made at 2h and 4h after delivery and at 8 am the following day. [Only data of 8 am the following day were extracted]	Early suckling: mothers were encouraged to breast-feed as soon as possible after birth. The babies were clothed and were not in skin-to-skin contact with the mother Control group: babies were placed in a cot with a heated mattress and the normal ward routine followed.	early suckling = within 33 min of birth (mean time of first suckling: 13.56±5.35 min after birth)

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Mortality				
Neonatal mortality risk	Late vs early breast feeding	Statistically significant: 75/3079 vs 70/7868 § aOR: 2.40, 95%CI [1.69; 3.40], p<0.0001 *In favour of early breastfeeding*	1, 3079 vs 7868	Edmond, 2006
Infection-specific mortality		Statistically significant: 52/3076 vs 41/7866 § aOR: 2.61, 95%CI [1.68; 4.04], p<0.0001 *In favour of early breastfeeding*	1, 3076 vs 7866	Edmond, 2007
Noninfection-specific mortality		Not statistically significant: 20/3076 vs 27/7866 § aOR: 1.63, 95%CI [0.85; 3.11], p=0.15 ¥		
Postneonatal mortality		Not statistically significant: No raw data available RR: 0.90, 95%CI [0.59; 1.37], p>0.05 ¥	1, 345 vs 362	Gunnlaugsson, 1993
Body temperature				
temperature <36.5°C	Early suckling vs late breast feeding	Statistically significant: No raw data available OR: 0.322, 95%CI [0.146; 0.712], p=0.005 *In favour of early suckling*	1, 70 vs 67 §	van den Bosch, 1990

¥ Imprecision (large variability of results)
§ Imprecision (limited sample size or low number of events)

Quality of evidence

Mortality

Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations
Edmond, 2006	No	No	No, confounding factors are clearly described	No	
Edmond, 2007	No	No	No, confounding factors are clearly described	No	
Gunnlaugsson, 1993	No	No	Unclear	No	

Body temperature

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
van den Bosch, 1990	No, blocked randomization method performed by an independent observer	Yes, but not possible	No	No, loss to follow-up explained	

Mortality

	Initial grading Low [C]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Large variability of results or low number of events
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Body temperature

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	limited sample size
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Moderate [B]**	

Conclusion	**Mortality** There is limited evidence in favour of early breast feeding. It was shown that early breast feeding (< 1 day) resulted in a statistically significant decrease of neonatal mortality risk and infection-specific mortality, compared to late breast feeding (Edmond 2006, Edmond 2007). A statistically significant decrease of noninfection-specific mortality or postneonatal mortality, using early breast feeding compared to late breast feeding, could not be demonstrated (Edmond 2007, Gunnlaugsson 1993. Evidence is of very low quality and results cannot be considered precise due to large variability of results. **Body temperature** There is limited evidence in favour of early breastfeeding (<33 min of birth). It was shown that early breast feeding resulted in a statistically significant decrease of newborns with a body temperature <36.5°C, compared to controls (van den Bosch 1993). Evidence is of moderate quality and results cannot be considered precise due to limited sample size.
Reference(s)	**Articles** Edmond KM, Zandoh C, Quigley MA, Amenga-Etego S, Owusu-Agyei S, Kirkwood BR. *Delayed breastfeeding initiation increases risk of neonatal mortality*. Pediatrics 2006, 117(3):e380-6 Edmond KM, Kirkwood BR, Amenga-Etego S, Owusu-Agyei S, Hurt LS. *Effect of early infant feeding practices on infection-specific neonatal mortality: an investigation of the causal links with observational data from rural Ghana.* Am J Clin Nutr 2007, 86:1126-31 Gunnlaugsson G, da Silva MC, Smedman L. *Age at breast feeding start and postneonatal growth and survival*. Archives of Disease in Childhood 1993, 69: 134-137 van den Bosch CA, Bullough CHW. *Effect of early suckling on term neonates' core body temperature*. Annals of Tropical Paediatrics 1990, 10:347-353

Bijlage 8: ES Bleeding – Keeping warm

Question (PICO)	In humans with severe bleeding/trauma (P) is not keeping the victim warm (RF) a risk factor for increased blood loss, complications or mortality (O) compared to keeping the victim warm (C)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the search terms: 1. [mh "Abdominal injuries"] or [mh "Multiple Trauma"] or [mh "Shock, Traumatic"] or [mh "Thoracic Injuries"] or [mh "Wounds, Nonpenetrating"] or [mh "Wounds, Penetrating"] or [mh Lacerations] or [mh "Vascular System Injuries"] or (trauma):ti,ab,kw or (traumatic NEXT injur*):ti,ab,kw or (bleeding):ti,ab,kw 2. hot:ti,ab,kw or warm:ti,ab,kw or Heat:ti,ab,kw or hot:ti,ab,kw or warm:ti,ab,kw or [mh "hypothermia"] or Hypothermia:ti,ab,kw or (body NEXT temperature):ti,ab,kw OR thermostasis:ti,ab,kw OR thermogenesis:ti,ab,kw 3. 1-2 AND **MEDLINE** (via PubMed interface) for guidelines, systematic reviews or experimental studies using the following search strategy: 1. "Hemorrhage"[Mesh] OR hemoorhage*[TIAB] OR bleeding[TIAB] OR Trauma[TIAB] OR traumatic injur*[TIAB] OR "lacerations"[Mesh] OR "wounds,nonpenetrating"[Mesh] OR laceration*[TIAB] OR "nonpenetrating wound"[TIAB] OR "nonpenetrating wounds"[TIAB] OR "nonpenetrating injury"[TIAB] OR "nonpenetrating injuries"[TIAB] OR "blunt injury"[TIAB] OR "blunt injuries"[TIAB] 2. Heat*[TIAB] OR hot[TIAB] OR warm*[TIAB] OR "Hot Temperature/therapeutic use"[Mesh] Or "Rewarming" [Mesh] OR "Hypothermia"[Mesh] OR Hypothermia[TIAB] OR "body temperature"[TIAB] OR thermostasis[TIAB] OR thermogenesis[TIAB] 3. "First Aid"[Mesh] OR "Community Health Workers"[Mesh] OR "Emergency Treatment"[Mesh:NoExp] OR "Emergency Medical Services"[Mesh:NoExp] OR "Emergency Service, Hospital"[Mesh] OR "Poison Control Centers"[Mesh] OR "Transportation of Patients"[Mesh] OR "Primary Health Care"[Mesh:NoExp] OR "Acute disease"[Mesh] OR "emergencies" [Mesh] OR "self care"[Mesh] OR "acute management" [TIAB] OR "immediate care" [TIAB] OR "prehospital treatment" [TIAB] OR "first aid"[TIAB] OR "self care"[TIAB] OR emergenc*[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) for systematic reviews or experimental studies using the following search strategy: 1. 'penetrating trauma'/exp OR 'laceration'/exp OR 'blunt trauma'/exp OR 'bleeding'/exp OR laceration*:ab,ti OR 'nonpenetrating wound':ab,ti OR 'nonpenetrating wounds':ab,ti OR 'nonpenetrating injury':ab,ti OR 'nonpenetrating injuries':ab,ti OR 'blunt injury':ab,ti OR 'blunt injuries':ab,ti OR hemorrhage*:ab,ti OR bleeding*:ab,ti OR 'bleeding'/exp OR Trauma:ab,ti OR (traumatic NEXT/1 injur*):ab,ti 2. Heat*:ab,ti OR hot:ab,ti OR warm*:ab,ti OR 'heat'/exp OR 'hypothermia'/exp OR hypothermia:ab,ti OR 'body temperature': ab,ti OR thermostasis:ab,ti OR thermogenesis:ab,ti 3. 'first aid'/exp OR 'health auxiliary'/exp OR 'emergency treatment'/de OR 'emergency health service'/exp OR 'poison center'/exp OR 'patient transport'/exp OR 'primary health care'/exp OR 'acute disease'/exp OR 'emergency'/exp OR 'self care'/exp OR 'acute management':ab,ti OR 'immediate care':ab,ti OR 'prehospital treatment':ab,ti OR 'self care':ab,ti OR 'first aid':ab,ti OR emergenc*:ab,ti Selected articles were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	12-03-2015
In/Exclusion criteria	**Population**: Include: sick or injured people or healthy volunteers of all ages. **Intervention**: Include: interventions provided by lay people (i.e. basic first responders, lay caregivers and/or community health workers). When the intervention is feasible to be performed by lay people but performed by a healthcare professional in the study, the study will be included in case no other evidence with laypeople is available (but considered as indirect evidence). Exclude: diagnostic procedures based on clinical signs/symptoms. Interventions that require special equipment or

	competences. Interventions that do not take place during the acute phase which can be considered as aftercare. **Outcome**: Include: Primary outcomes: mortality, blood loss, complications such as organ failure, respiratory syndromes, shock, coma, inflammation, sepsis, cardiac arrest. Exclude: Secondary outcomes: days in hospital, duration of ventilation; measures of performance by basic first responders or lay caregivers and/or community health workers. **Design**: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies. **Language**: Include: English **Publication year**: Include: all years

Characteristics of included studies

Author, Year, Country	Study design	Population	Comparison	Remarks
Arthurs, 2006, USA	Observational: Cross-sectional study	2848 patients (2762 males, 86 females), mean age 28±10 years, with an initial temperature recording on arrival at Combat Surgical Hospital between January 2004 and December 2004. 82% was normothermic (n=2335), 16% was mildly hypothermic (n=455), 2% was moderately (n=57) and 0.2% severly hypothermic (n=5)	1. Mild hypothermia: T=34-36°C 2. Moderate-severe hypothermia: T<34°C 3. Normothermia: T>36°C	
Beilman, 2009, USA	Observational: cross-sectional study	383 adult patients (279 male, 104 female), mean age 39±17 years, from 7 level I trauma centers, who were admitted to emergency department (between October 2004 and February 2006) within 6 hours of injury and had packed red blood cells transfused in the field or within 6 hours of arrival to ED. 155 had hypothermia, 204 had no hypothermia	- Hypothermia: T<35°C - No hypothermia: T≥35°C	
Bukur, 2012, USA	Observational: cross-sectional study	21023 patients (15389 male, 5634 female), mean age 39.9±19.5 years, in the Los Angeles County Trauma System Database (data between 2005-2009) with available temperature, transfusion and outcome data available. 11642 had hypothermia, 9381 had normal temperatures.	- Hypothermia: T<36.5 - Normothermic: T≥36.5	
Ireland, 2011, Australia	Observational: cross-sectional study	732 patients (556 male, 176 female), mean age 45.8±20.6 years, with major trauma (mean Injury Severity Score (ISS) of 22), identified from Alfred Health's trauma registry of which 97 were	- Hypothermia: T<35°C - Normothermia: 35°C≤T≤37.5°C	

		hypothermic and 584 had normal temperature.		
Martin, 2005, USA	Observational: cross-sectional study	700,304 patients extracted from the National Trauma Data Bank with an admission temperature recorded of which 11,026 had hypothermia (mean age 39.4±22.4; 7580 male/3446 female) and 689,278 had normal temperatures (mean age 37.8±22.9; 451,596 male/237,682 female)	- Hypothermia: T<35°C - Normothermia: T≥35°C	
Mommsen, 2013, Germany	Observational: Cross-sectional study	310 patients, mean age 41.9±17.5 (220 male, 90 female), with multiple injuries (ISS≥16) who were treated at the level 1 Trauma centre between January 2005 and March 2009. 114 patients had hypothermia, 196 patients had normal temperatures	- Hypothermia: T<35°C - Normothermia: T≥35°C	
Seekamp, 1995, Germany	Observational: cross-sectional study	641 trauma patients with ISS >25 who were admitted between 1988 and 1993. 400 patients had a T≥34°C, 226 patients had a T<34°C	- Hypothermia: T<34°C - Normothermia: T≥34°C	
Shafi, 2005, USA	Observational: Cross-sectional study	38,550 patients from the National Trauma Databank (study period: 1994-2002), mean age 34±10 years (29265 men, 9285 women)	- Hypothermia: T<35°C - Normothermia: T≥35°C	
Sundberg, 2011, USA	Observational: cross-sectional study	190 pediatric trauma patients (<17 years, 118 male/72 female) who presented to the pediatric emergency department of a tertiary, urban level 1 children's trauma center between September 2006 and March 2008.	- Hypothermia: T<35°C - Normothermia: T≥35°C	
Thompson, 2010, USA	Observational: cross-sectional study	147 patients admitted to a level I trauma center following severe traumatic brain injury from January 2000 to January 2002. Mean age of hypothermic patients (n=59) was 34.9±2.3 years; mean age of normothermic patients (n=88) was 37.5±2.0 years.	- Hypothermia: T<35°C - Normothermia: T≥35°C	
Waibel, 2010, USA	Observational: cross-sectional study	1629 patients admitted to the rural level I trauma center between July 2002 and June 2007 with injury. 182 patients were hypothermic, 1447 were normothermic.	- Hypothermia: T<36°C - Normothermia: T≥36°C	
Wang, 2005	Observational: cross-sectional study	Data of 38520 trauma patients between January 2000 and December 2002 extracted from the Pennsylvania Trauma Outcome Study. 1921 patients had a temperature ≤35°C (1353 males, 568 females) and 36599 patients had normal temperature (22519 males, 14080 females)	- Hypothermia: T≤35°C - Normothermia: T>35°C	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Mortality				

Mortality	Hypothermia (T<36°C) vs normothermia	Statistically significant: 45/509 vs 46/2334 OR: 4.82, 95%CI [3.16; 7.36] P<0.00001* *In favour of normothermia*	1, 509 vs 2334	Arthurs, 2006
	Hypothermia (T<35°C) vs no hypothermia	Not statistically significant: 25/152 vs 25/204 £ p=0.2826	1, 152 vs 204 §	Beilman, 2009
	Hypothermia (T<36.5°C) vs no hypothermia	Statistically significant: 516/9381 vs 396/11642 OR: 1.3, 95%CI [1.2; 1.4] p<0.001 *In favour of no hypothermia*	1, 9381 vs 11642	Bukur, 2012
	Hypothermia (T<35°C) vs no hypothermia	Statistically significant: 29/97 vs 35/584 OR: 6.7, 95%CI [3.87; 11.55] p<0.001 *In favour of no hypothermia*	1, 97 vs 584 §	Ireland, 2011
		Statistically significant: 2812/11026 vs 20678/689278 £ p<0.001 *In favour of no hypothermia*	1, 11026 vs 689278	Martin, 2005
		Statistically significant: 16/114 vs 11/196 £ p=0.020 *In favour of no hypothermia*	1, 114 vs 196 §	Mommsen, 2013
	Hypothermia (T<34°C) vs no hypothermia	Statistically significant: 109/226 vs 114/400 OR: 2.34, 95%CI [1.66; 3.28] p<0.00001* *In favour of no hypothermia*	1, 226 vs 400 §	Seekamp, 1995
	Hypothermia (T<35°C) vs no hypothermia	Statistically significant: OR: 1.19, 95%CI [1.05; 1.35], p=0.008 *In favour of no hypothermia*	1, 3267 vs 35283	Shafi, 2005
		Statistically significant: Adjusted for seasonal variation: OR: 9.2, 95%CI [3.2; 26.2], p<0.0001 *In favour of no hypothermia* Adjusted for mode of transportation (ground vs air): OR: 8.7, 95%CI [3.1; 24.6], p<0.0001 *In favour of no hypothermia*	1, 22 vs 168 §	Sundberg, 2011
	Hypothermia (T<36°C) vs no hypothermia	Statistically significant: aOR: 2.41, 95%CI [1.12; 5.22], p=0.025 *In favour of no hypothermia*	1, 182 vs 1447	Waibel, 2010
	Hypothermia (T≤35°C) vs no hypothermia	Statistically significant: OR: 3.03, 95%CI [2.62; 3.51], p<0.00001 *In favour of no hypothermia*	1, 36599 vs 1921	Wang, 2005
Blood loss				
Estimated blood loss (mL)	Mild hypothermia vs normothermia	Statistically significant: 806±1206 vs 370±910 MD: 436.0, 95%CI [319.20; 552.80], p<0.00001* *In favour of normothermia*	1, 455 vs 2335	Arthurs, 2006
	Moderate-severe hypothermia vs normothermia	Statistically significant: 1317±2581 vs 370±910 MD: 947.0, 95%CI [303.49; 1590.51], p<0.004*	1, 62 vs 2335	

		In favour of normothermia		
Total transfusion volume (mL)	Hypothermia (T<36.5°C) vs no hypothermia	Statistically significant: 935.7±3110 vs 562.7±2200 MD: 373.00, 95%CI [301.0; 444.9], p<0.001 *In favour of no hypothermia*	1, 9381 vs 11642	Bukur, 2012
Transfusion of packed red blood cells (units)	Mild hypothermia vs normothermia	Statistically significant: 6.5±5 vs 4.8±5 MD: 1.7, 95%CI [1.19, 2.21] p<0.00001* *In favour of normothermia*	1, 455 vs 2335	Arthurs, 2006
	Moderate-severe hypothermia vs normothermia	Statistically significant: 9.6±9 vs 4.8±5 MD: 4.80, 95%CI [2.55, 7.05] p<0.0001* *In favour of normothermia*	1, 62 vs 2335	
	Hypothermia (T<35°C) vs no hypothermia	Not statistically significant: OR: 1.05, 95%CI [0.99; 1.10] p=0.088	1, 69 vs 49	Ireland, 2011
		Statistically significant: 18.2±19.2 vs 11.5±14.5 MD: 6.70, p=0.005 £ *In favour of no hypothermia*	1, 114 vs 196 §	Mommsen, 2013
Transfusion of packed red blood cells (mL)		Statistically significant: 3281±4242 vs 1543±2094 MD: 1738.0, p<0.0001 £ *In favour of no hypothermia*	1, 155 vs 204	Beilman, 2009
Transfusion of fresh frozen plasma (units)	Mild hypothermia vs normothermia	Statistically significant: 5.5±4 vs 4.9±5 MD: 0.60, 95%CI [0.18, 1.02] p<0.005* *In favour of normothermia*	1, 455 vs 2335	Arthurs, 2006
	Hypothermia (T<35°C) vs no hypothermia	Statistically significant: 12.5±14.1 vs 7.6±11.5 MD: 4.90, p<0.001£ *In favour of no hypothermia*	1, 114 vs 196 §	Mommsen, 2013
		Not statistically significant: OR: 1.00, 95%CI [0.99; 1.00] p=0.135	1, 44 vs 39	Ireland, 2011
Transfusion of platelets (units)		Statistically significant: 2.1±3.4 vs 1.1±3.6 MD: 1.00, p<0.001 £ *In favour of no hypothermia*	1, 114 vs 196 §	Mommsen, 2013
		Not statistically significant: OR: 0.95, 95%CI [0.82; 1.11] p=0.531	1, 25 vs 22	Ireland, 2011
Complications				
Shock (SBP < 90 mmHg)	Hypothermia (<36°C) vs no hypothermia	Statistically significant: OR: 5.7, 95%CI [4.0, 8.0] p<0.01 *In favour of no hypothermia*	1, 517 vs 2335	Arthurs, 2006
	Hypothermia (<36.5°C) vs no hypothermia	Statistically significant: 460/9335 vs 273/11622 p<0.001 £ *In favour of no hypothermia*	1, 9335 vs 11622	Bukur, 2012
	Hypothermia (T<36°C) vs no hypothermia	Statistically significant: 21/182 vs 46/1447 p<0.001 £ *In favour of no hypothermia*	1, 182 vs 1447	Waibel, 2010

Glasgow Coma Scale	1. Mild hypothermia 2. Moderate-severe hypothermia 3. Normothermia	Statistically significant: Mild hypothermia vs normothermic: 12.6±4.4 vs 13.9±3.1 MD: -1.30, 95%CI [-1.72, -0.88] p<0.00001* *In favour of normothermia*	1, 455 vs 2335	Arthurs, 2006
		Statistically significant: Moderate-severe hypothermia vs normothermic: 7.7±5.6 vs 13.9±3.1 MD: - 6.20, 95%CI [-7.60, -4.80] p<0.00001* *In favour of normothermia*	1, 62 vs 2335	
	Hypothermia (T<35°C) vs no hypothermia	Statistically significant: 10.8 vs 14.2 MD: -3.4 £ p<0.001 *In favour of no hypothermia*	1, 11026 vs 689278	Martin, 2005
		Statistically significant: 6.3±0.4 vs 7.8±0.3 MD: -1.50 £ p<0.01 *In favour of no hypothermia*	1, 59 vs 88 §	Thompson, 2010
	Hypothermia (T<36°C) vs no hypothermia	Statistically significant: 9.3 vs 13.2 MD: -3.9, p<0.001 £ *In favour of no hypothermia*	1, 182 vs 1447	Waibel, 2010
Glasgow Coma Scale ≤8		Statistically significant: OR: 3.4, 95%CI [2.6; 4.3] p<0.01 *In favour of no hypothermia*	1, 517 vs 2335	Arthurs, 2006
	Hypothermia (<36.5°C) vs no hypothermia	Statistically significant: 770/9256 vs 688/11480 p<0.001 £ *In favour of no hypothermia*	1, 9256 vs 11480	Bukur, 2012
	Hypothermia (T<35°C) vs no hypothermia	21/22 vs 63/168 OR: 35.00, 95%CI [4.60; 266.56] p=0.0006* *In favour of no hypothermia*	22 vs 168	Sundberg, 2011
Multiple Organ Dysfunction Syndrome (MODS)		Statistically significant: 28/134 vs 17/187 OR: 2.64, 95%CI [1.38; 5.06] p=0.003* *In favour of no hypothermia*	1, 134 vs 187 §	Beilman, 2009
		Not statistically significant: 16/114 vs 13/196 P=0.486 £	1, 114 vs 196 §	Mommsen, 2013
Adult Respiratory Distress Syndrome (ARDS)	Hypothermia (<36.5°C) vs no hypothermia	Statistically significant: 236/9381 vs 178/11642 OR: 1.3, 95%CI [1.2; 1.5] p<0.001 *In favour of no hypothermia*	1, 9381 vs 11642	Bukur, 2012
	Hypothermia (T<35°C) vs no hypothermia	Statistically significant: 111/3267 vs 529/35283 OR: 2.31, 95%CI [1.88; 2.84] p<0.00001* *In favour of no hypothermia*	1, 3267 vs 35283	Shafi, 2005
	Hypothermia (T<36°C) vs no hypothermia	Not statistically significant: 2/182 vs 9/1447 p=0.353 £	1, 182 vs 1447	Waibel, 2010
Pneumonia	Hypothermia (<36.5°C) vs no hypothermia	Statistically significant: 388/9381 vs 334/11642 OR: 1.5, 95%CI [1.3; 1.7] p<0.001 *In favour of no hypothermia*	1, 9381 vs 11642	Bukur, 2012

	Hypothermia (T<35°C) vs no hypothermia	Statistically significant: 392/3267 vs 1764/35283 OR: 2.59, 95%CI [2.31; 2.91] p<0.00001* *In favour of no hypothermia*	1, 3267 vs 35283	Shafi, 2005
Respiratory failure	Hypothermia (T<36°C) vs no hypothermia	Statistically significant: 28/182 vs 84/1447 p<0.001 £ *In favour of no hypothermia*	1, 182 vs 1447	Waibel, 2010
Systemic Inflammatory Response Syndrome (SIRS)	Hypothermia (T<35°C) vs no hypothermia	Not statistically significant: 96/114 vs 144/196 p=0.091 £	1, 114 vs 196 §	Mommsen, 2013
Sepsis		Not statistically significant: 56/114 vs 77/196 p=0.188 £		
Infections		Statistically significant: 490/3267 vs 2470/35283 OR: 2.34, 95%CI [2.11; 2.60] p<0.00001* *In favour of no hypothermia*	1, 3267 vs 35283	Shafi, 2005
Any complications		Statistically significant: 817/3267 vs 3881/35283 OR: 2.70, 95%CI [2.48; 2.94] P<0.00001* *In favour of no hypothermia*		
Cardiac arrest		Statistically significant: 49/3267 vs 141/35283 OR: 3.80, 95%CI [2.74; 5.26] P<0.00001* *In favour of no hypothermia*		
Number of complications during hospitalization		Statistically significant: 2.3±0.2 vs 1.3±0.2 MD: 1.00, 95%CI [0.93; 1.07] P<0.00001* *In favour of no hypothermia*	1, 59 vs 88 §	Thompson, 2010

§ Imprecision (limited sample size)
£ No CI calculated because unable to adjust for confounding factors

Quality of evidence:

Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations
Arthurs, 2006	No	No	Yes, no data on time of year, time of injury, time for extrication and time to evacuation	No	
Beilman, 2009	No	No	No	No	
Bukur, 2012	Yes, differences in age, % penetrating injury	No	Unclear	No	Causation cannot be definitively established, prehospital scene and transport time were not analyzed,…
Ireland, 2011	No	No	No, confounders are well described and	No	

			accounted in calculations		
Martin, 2005	Yes, differences in age, gender, % penetrating injury	No	Unclear, "while corrected for confounders" but not stated which confoundes	No	
Mommsen, 2013	No	No	No, confounders are described and accounted in calculations	No	
Seekamp, 1995	Unclear, demographic data of groups not mentioned	No	Unclear, not mentioned	No	
Shafi, 2005	No, no differences in age or gender	No	Unclear, not mentioned	No	
Sundberg, 2011	Yes, differences in age, but no differences in gender	No	No, they accounted for seaon and mode of transportation	No	
Thompson, 2010	No, no differences in age or gender	No	Unclear	No	
Waibel, 2010	No, no differences in age or gender	No	Unclear	No	
Wang, 2005	No, differences in gender	No	No, adjusted for age, ISS, injuries, blood pressure and temperature measurement route	No	

	Initial grading Low [C]	Downgrading due to
Limitations of study design	-1	See table 'Quality of evidence'
Imprecision	0	
Inconsistency	0	
Indirectness	0	
Publication bias	0	
QUALITY (GRADE)	**Final grading Very low [D]**	

Conclusion(s)	There is limited evidence from 12 observational studies with harm for hypothermia. (In making this evidence conclusion, we place a higher value over the significant outcomes of larger studies) **Mortality** It was shown that hypothermia resulted in a statistically significant increased risk of death, compared to no hypothermia (Arthurs 2006, Beilman 2009, Bukur 2012, Ireland 2011, Martin 2005, Mommsen 2013, Seekamp 1995, Shafi 2005, Sundberg, Waibel 2010, Wang 2005). **Blood loss** It was shown that hypothermia resulted in a statistically significant increased risk of blood loss, total transfusion volume, transfusion of packed red blood cells, transfusion of fresh frozen plasma and transfusion of platelets, compared to no hypothermia (Arthurs 2006, Beilman 2009, Bukur 2012, Ireland 2011, Martin 2005, Mommsen 2013, Seekamp 1995, Shafi 2005, Sundberg, Waibel 2010, Wang 2005).

	Complications It was shown that hypothermia resulted in a statistically significant increased risk of complications, such as shock, coma, multiple organ disfunction syndrome, ARDS, pneumonia, respiratory failure, SIRS, sepsis, infections and cardiac arrest, compared to no hypothermia (Arthurs 2006, Beilman 2009, Bukur 2012, Ireland 2011, Martin 2005, Mommsen 2013, Seekamp 1995, Shafi 2005, Sundberg, Thompson, Waibel 2010, Wang 2005). Evidence is of very low quality.
Reference(s)	**Articles:** Arthurs Z, Cuadrado D, Beekley A, Grathwohl K, Perkins J, Rush R, Sebesta J. *The impact of hypothermia on trauma care at the 31st combat support hospital*. Am J Surg 2006, 191:610-614 Beilman GJ, Blondet JJ, Nelson TR, Nathens AB, Moore FA, Rhee P, Puyana JC, Moore EE, Cohn SM. *Early hypothermia in severly injured trauma patients is a significant risk factor for multiple organ dysfunction syndrome but not mortality.* Ann Surg 2009, 249:845-850 Bukur M, Hadjibashi AA, Ley EJ, Malinoski D, Singer M, Barmparas G, Margulies D, Salim A. *Impact of prehospital hypothermia on transfusion requirements and outcomes*. J Trauma Acute Care Surg 2012, 73(5):1195-1201 Ireland S, Endacott R, Cameron P, Fitzgerald M, Paul E. *The incidence and significance of accidental hypothermia in major trauma – A prospective observational study*. Resuscitation 2011, 82:300-306 Martin RS, Kilgo PD, Miller PR, Hoth J, Meredith JW, Chang MC. *Injury-associated hypothermia: an analysis of the 2004 National Trauma Data Bank*. Schock 2005, 24(2):114-118 Seekamp A, Ziegler M, Van Griensven M, Grotz M, Regel G. *The role of hypothermia in trauma patients*. Eur J Emerg Med 1995, 2:28-32 Shafi S, Elliott AC, Gentilello L. *Is hypothermia simply marker of shock and injury severity or an independent risk factor for mortality in trauma patients? Analysis of a large National Trauma Registry.* J Trauma 2005, 56:1081-1085 Sundberg J, Estrada C, Jenkins C, Ray J, Abramo T. *Hypothermia is associated with poor outcome in pediatric trauma patients*. Am J Emerg Med 2011, 29:1019-1022 Thompson HJ, Kirkness CJ, Mitchell PH. *Hypothermia and rapid rewarming is associated with worse outcome following traumatic brain injury.* J Trauma Nurs 2010, 17(4):173-177 Waibel BH, Durham CA, Newell MA, Schlitzkus LL, Sagraves SG, Rotondo MF. *Impact of hypothermia in the rural, pediatric trauma patient.* Pediatr Crit Care Med 2010, 11(2):199-204 Wang HE, Callaway CW, Peitzman AB. *Admission hypothermia and outcome after major trauma*. Crit Care Med 2005, 33:1296-1301

Bijlage 9: ES Cardiac arrest: Palpation pulse rate

Question (PICO)	Among persons with a suspected cardiac arrest (P), is palpation of the radial pulse (wrist) (I) more accurate to evaluate the heart rate/rhythm (O) compared to the palpation of the carotid pulse (neck) (C)?
Search Strategy	Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: 1. carotid:ti,ab,kw OR radial:ti,ab;kw OR wrist:ti,ab,kw OR neck:ti,ab,kw 2. [mh pulse] OR pulse:ti,ab,kw OR 'heart rate':ti,ab,kw 3. [mh palpation] OR palp*:ti,ab,kw OR feel:ti,ab,kw OR take:ti,ab,kw 4. 1-3 AND **MEDLINE** (via PubMed interface) for experimental and observational studies using the following search strategy: 1. "carotid arteries"[Mesh] OR "radial artery"[Mesh] OR carotid[TIAB] OR radial[TIAB] OR wrist[TIAB] OR neck[TIAB] 2. "Heart Rate/physiology"[Mesh] OR "heart rate"[TIAB] OR "pulse"[Mesh] OR "pulse"[TIAB] 3. palpation[Mesh] OR palp*[tiab] OR "feel"[tiab] OR "take"[tiab] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1.'carotid'/exp OR 'carotid':ab,ti OR 'radial':ab,ti OR 'wrist':ab,ti OR 'neck':ab,ti 2.'pulse rate'/exp OR 'pulse':ab,ti 3.'palpation'/exp OR palp*:ab,ti OR 'feel':ab,ti OR 'take':ab,ti 4. 1-3 AND Included articles, retrieved with the above searches, were used to identify other studies by searching (1) reference lists and (2) 20 first related citations in **MEDLINE** (via PubMed interface).
Search date	22/01/2015
In/Exclusion criteria	**Population:** sick or injured people or healthy volunteers. Infants were excluded. **Intervention:** Include: palpation of radial/carotid pulse rate, Exclude: palpation of pulse rates at other arteries (femoral, brachial (infants),…) **Comparison:** Include: studies that compare radial/carotid pulse rate versus reference method (ECG monitoring), if no comparison with a reference test is available, also studies that compare radial versus carotid pulse rates were included Exclude: studies not including palpation of both radial and carotid pulse rate. **Outcome:** Include: heart/pulse rate, diagnostic-related outcomes such as sensitivity, specificity, positive/negative predictive value, patient-important outcomes (mortality, morbidity, symptoms, quality of life and resource use). **Study design:** Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched. An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available. An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available. Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies.

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
DeVan, 2005, USA	Diagnostic: accuracy study	Twenty young physically active adults (age: 18-31 years, 14 men and 6 women) performed 2 sets of submaximal exercises	Test: radial/carotid pulse count post-exercise (15-30s after exercise) 1. Moderate intense exercise (70% HR_{max})	Pulse rates at other moments (i.e. during and immediately after exercise) were not

		for 5 minutes at 70% and 85% of maximal HR on the treadmill (with ECG registration); one with carotid pulse count and another with radial pulse count (i.e., a total of 4 submaximal runs). Carotid and radial pulse count trials were randomized.	2. High intense exercise (85% HR_{max}) Reference test: ECG registration of the HR	included because the least relevant towards PICO question. Effect size: although raw data are not available, data are clearly depicted in figure 1 and figure 2 and summarized in the text. Therefore, no downgrading for imprecision (due to lack of data) was performed.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Heart rate (bpm) (post- moderate intense exercise (70% HR_{max})	Radial/carotid pulse count versus ECG-derived HR	Radial palpation: Not statistically significant: no raw data available (see 'remarks').	1, 20 vs 20 §	DeVan,2005
		Carotid palpation: Not statistically significant: no raw data available (see 'remarks').		
Heart rate (bpm) (post- high intense exercise (85% HR_{max})		Radial palpation: Statistically significant: MD: -10, 95% CI not available in text (see 'remarks') ($p<0.05$)		
		Carotid palpation: Not statistically significant: no raw data available (see 'remarks').		

§ Imprecision (limited sample size)

Quality of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	
Imprecision	-1	Limited sample size
Inconsistency	0	
Indirectness	-1	Outcome (absence of direct evidence about impact on patient-important outcomes), Population (difference between studies population (physically active adults) versus target population for the recommendation (cardiac arrest)
Publication bias	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	Post-exercise at moderate intensity (70% HR_{max}) There is limited evidence from 1 accuracy study, showing that both palpation of the radial pulse and the carotid pulse are accurate tests for measuring heart rate (DeVan,2005). A statistically significant difference in heart rate, using carotid/radial pulse rates compared to ECG-derived heart rate (reference test), could not be demonstrated. Post-exercise at high intensity (85% HR_{max}) There is limited evidence from 1 accuracy study, showing that palpation of the carotid pulse was more accurate for measuring heart rate than palpation of the radial pulse (DeVan,2005). It was shown that the palpation of the radial pulse resulted in a statistically significant lower heart rate (~10 beat per minute) , compared to ECG-derived heart rate. No statistical difference was observed between carotid pulse or ECG-derived heart rate after high-intense exercise. Evidence is of low quality and results of this study are imprecise due to limited sample size.
Reference(s)	DeVan AE, Lacy BK, Cortez-Cooper MY, Tanaka H. *Post-exercise palpation of pulse rates: its applicability to habitual exercisers.* Scan J Med Sci Sports 2005, 15:177-181