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Systematic Review

Effectiveness of insecticide-treated and untreated nets to prevent malaria in India†

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Abstract

OBJECTIVES India is the most malaria-endemic country in South-East Asia, resulting in a high socio-economic burden. Insecticide-treated or untreated nets are effective interventions to prevent malaria. As part of an Indian first-aid guideline project, we aimed to investigate the magnitude of this effect in India.
METHODS We searched MEDLINE, Embase and Central to systematically review Indian studies on the effectiveness of treated or untreated *vs.* no nets. Parasite prevalence and annual parasite incidence served as malaria outcomes. The overall effect was investigated by performing meta-analyses and calculating the pooled risk ratios (RR) and incidence rate ratios.
RESULTS Of 479 articles, we finally retained 16 Indian studies. Untreated nets decreased the risk of parasite prevalence compared to no nets [RR 0.69 (95% CI; 0.55, 0.87) in high-endemic areas, RR 0.49 (95% CI; 0.28, 0.84) in low-endemic areas], as was the case but more pronounced for treated nets [RR 0.35 (95% CI; 0.26, 0.47) in high-endemic areas, risk ratio 0.16 (95% CI; 0.06, 0.44) in low-endemic areas]. Incidence rate ratios showed a similar observation: a significantly reduced rate of parasites in the blood for untreated nets *vs.* no nets, which was more pronounced in low-endemic areas and for those who used treated nets. The average effect of treated nets (*vs.* no nets) on parasite prevalence was higher in Indian studies (RR 0.16–0.35) than in non-Indian studies (data derived from a Cochrane systematic review; RR 0.58–0.87).
CONCLUSIONS Both treated and untreated nets have a clear protective effect against malaria in the Indian context. This effect is more pronounced there than in other countries.

keywords malaria, insecticide-treated bed nets, mosquito nets, India, primary prevention, systematic review

Introduction

Malaria is one of the major vectorborne diseases in South-East Asia. Despite the rapid decline in malaria incidence in recent years, WHO estimates indicate that India is the most malaria-endemic country in South-East Asia with 881.730 cases and 440 deaths reported in 2013 [1]. This results in a high social and economic burden including effects on fertility, population growth, saving and investment, worker productivity, absenteeism and medical costs [2].

Vector control is the main way to reduce malaria transmission in the community. Indoor residual spraying (IRS) or insecticide-treated bed nets and curtains (also known as insecticide-treated nets, TNs) are preventive measures to combat malaria [3].

A recent study in the malaria-endemic area of Sundargarh District in Orissa showed that IRS or TNs had the same epidemiological impact, suggesting that none of these interventions could be seen as superior in terms of effectiveness [4]. However, in the Indian context, the use of TN, but also untreated nets (UN), seems more appropriate than IRS. Indeed, TNs are easy to distribute and explain by community health workers and have the added advantage that no specific equipment is required (unlike for IRS). The recommendation to use TN should apply to the general Indian population with extra attention to the so-called high-malaria states (Orissa,

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Chhattisgarh, Jharkhand and the states in the far north-east of India) [5] and the rural areas, where medical services cannot be easily accessed and where about 90% of malaria deaths in India occur [6]. A community-based survey in 596 Indian respondents revealed that TNs could be considered safe and socially acceptable and should be promoted for malaria reduction [7].

A Cochrane systematic review and meta-analyses of studies performed outside India [8] already demonstrated that TNs are highly effective in reducing mortality and morbidity from malaria. However, because India has a wide topological and climatic diversity together with a wide species diversity of malaria vectors [9, 10], collecting the best available evidence of the effects of net usage from Indian studies is relevant and timely. Therefore, we conducted a systematic literature review to investigate the effectiveness of TN or UN, compared to no nets (NNs) to prevent malaria in India.

Method

We followed an evidence-based set of items (27-item checklist) for the reporting of systematic reviews and meta-analyses, as formulated by the PRISMA statement (Table S1) [11].

Search strategy

Eligible studies were identified by searching the following databases: Medline (PubMed interface), Embase (Embase.com interface) and the Cochrane Central Register of Controlled Trials. Detailed information about the search formula can be found in Data S1. Studies were independently selected by two reviewers (HVR and EDB). Titles and abstracts of the retrieved studies were screened. The full text of each article that potentially met the eligibility criteria was obtained, and after a full-text assessment, studies that did not meet the selection criteria were excluded. The first 20 related items of the included studies in PubMed were scanned for other potentially eligible studies. The reviewers compared their final selection of studies and resolved discrepancies by consensus. Once agreement had been reached, data of all included studies were extracted into predefined evidence summary tables as described before [12].

Eligibility criteria

Population. Studies performed in India with laypersons and/or community health workers were included. A layperson is defined as a person who does not have specialised or professional knowledge of a subject.

Intervention. Bed nets or curtains either treated with a synthetic pyrethroid insecticide (TN) or not (untreated nets, UN) were included. The minimum target impregnation dose of the TN was 200 mg/m^2 permethrin or etofenprox, 30 mg/m^2 cyfluthrin, 20 mg/m^2 alphacypermethrin or 10 mg/m^2 deltamethrin/lambdacyhalothrin. No distinction was made between insecticide-treated bed nets and curtains, which were assumed to have approximately the same impact [8].

Comparison. Only studies comparing UN and/or TN with no bed net or curtain usage (NN) were included.

Outcome. Parasite prevalence and annual parasite incidence were counted as malaria outcomes. Parasite prevalence was assessed via an epidemiological assessment that consisted of a door-to-door fortnightly surveillance where thick/thin blood smears from fever cases were investigated microscopically. Only the period after (un) treated bed nets were impregnated and divided was used to assess the parasite prevalence, which was defined as the proportion of the population in whom *Plasmodium* infection is detected at a particular time with a diagnostic test (usually microscopy or a rapid diagnostic test) [13]. Annual parasite incidence was calculated as the total number of positive slides for malarial parasites (*Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae, Plasmodium ovale*) among fever cases per 1000 population per year.

Study design. We included experimental [(cluster) randomised controlled trials, controlled clinical trials] or observational study designs (case–control studies and cohort studies). Narrative reviews, commentaries, letters and opinions were excluded.

Language. Studies in English, French, German or Dutch were included.

Search window. Studies from the date of inception of the databases until 16th of June 2014 were included.

Data collection

Data concerning study design, study population, trial location, duration and type of intervention, outcome measure and study findings were extracted.

Quality of evidence

The GRADE approach was used to grade the overall quality of evidence included in this review. GRADE considers limitations in study design of the included studies, inconsistency between the different studies (due to differences in populations, interventions or outcomes), indirectness (of population, intervention or outcome), imprecision and publication bias. Limitations in experimental study designs were analysed by evaluating the presence of lack of allocation concealment, lack of blinding, incomplete accounting of outcome events and selective outcome reporting. The quality of the evidence can be downgraded for each of the previous quality criteria and finally results in a high, moderate, low or very low level of evidence [14].

Statistical analysis

Statistical software was used to calculate the (unadjusted) risk ratio of the parasite prevalence (Review Manager 5.1) or the annual parasite incidence rate ratio (StatsDirect 2.8.0) in the intervention (TN or untreated nets) *vs.* the control group (no nets). We used data from the (first impregnated) post-intervention period to calculate these risk ratios and rate ratios. If no raw data on positive blood slides or parasite prevalence were available, an attempt to contact the authors via e-mail to request these data was made.

Mantel–Haenszel random-effects meta-analyses were performed to pool risk ratios and incidence rate ratios across studies. Subgroup analyses were carried out for low-endemic (annual parasite incidence ≤2) *vs.* high-endemic (annual parasite incidence >2) areas [15], for type of study design (clustered randomised controlled trials *vs.* controlled interrupted time series) and for the duration of the impregnation period (<1 year *vs.* ≥1 year). Heterogeneity was expressed by the I^2 statistic, which estimates the percentage of total variation between studies that is due to heterogeneity rather than chance. I^2 is calculated from basic results obtained from a typical meta-analysis as $I^2 = 100\%* (Q\text{-}df)/Q$, where Q is Cochran's heterogeneity statistic and df the degrees of freedom. Negative values of I^2 are put equal to zero so that I^2 lies between 0% and 100%. The following thresholds for the interpretation of I^2 can serve as a rough guide: 0–40% (might not be important), 30–60% (may represent moderate heterogeneity), 50–90% (may represent substantial heterogeneity) and 75–100% (considerable heterogeneity) [16].

Publication bias was assessed by visual inspection of funnel plots and by formal testing with Egger's linear regression method (StatsDirect 2.8.0).

Results

The systematic literature search resulted in a total of 479 abstracts. Figure 1 represents a flow chart describing the selection process used in the systematic review.

Study characteristics

Sixteen experimental Indian studies were finally included (Table S2). Four studies were performed in low-endemic areas (annual parasite incidence ≤2) of Uttar Pradesh [17–20], and 12 studies were carried out in high-endemic areas (annual parasite incidence >2) of Gujarat (n = 1) [21], Chhattisgarh (n = 1) [22], Orissa (n = 7) [23–29] and Assam (n = 3) [30–32] (Figure 2). The duration of the (first) impregnation period ranged from 8 to 12 months in the majority of the studies (n = 15). Five months was the shortest impregnation period [32] while 1 study made use of a 2-year impregnation period. One study made use of insecticide-treated window and door curtains [17], while insecticide-treated bed nets were used in all other studies (n = 15). The TNs were impregnated with deltamethrin (n = 6) [19, 21, 26, 29, 31, 32], lambdacyhalothrin (n = 4) [23–25, 28], alphacypermethrin (n = 3) [17, 18, 22] or permethrin (n = 3) [20, 27, 30] with a dose ranging from 10 to 1000 $mg*m^{-2}$. Six studies reported the use of long-lasting insecticide-treated nets aiming to have a long-term protection from malaria [19, 20, 22, 27, 30, 31]. An epidemiological evaluation based on surveillance for malaria cases was performed in all studies. From this, direct malaria-related outcomes, such as slide positivity rate (i.e. the number of blood slides with any malaria parasites divided by the total number of blood slides examined multiplied by 100) or the number of malaria cases (i.e. any case in which, regardless of the presence or absence of clinical symptoms, malaria parasites have been confirmed by quality-controlled laboratory diagnosis), were available for 15 studies and were used for meta-analyses. One study was removed from meta-analyses because raw data on these outcomes were not published [32]. The use of untreated nets (intervention) was compared with no nets (control) in 13 studies (four in low-endemic areas [17–20] and nine in high-endemic areas [21–29, 31]).

Quality of evidence

All included studies were experimental studies (seven controlled interrupted time series and nine cluster randomised controlled trials), which resulted in an initial 'high level of evidence'. Limitations in study design were present because the intervention/control groups were not

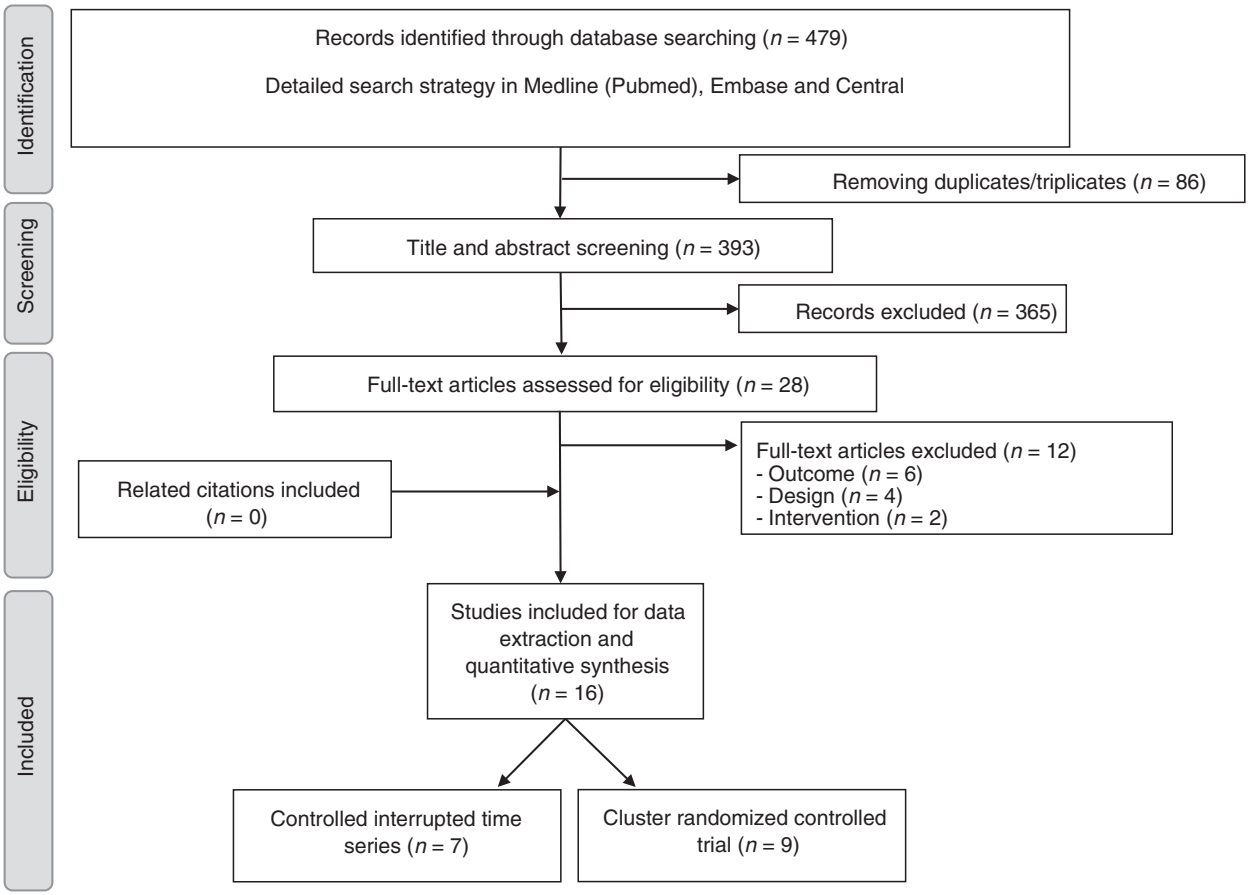

Figure 1 Flow chart describing the identification and inclusion of relevant studies.

randomised (in three of the four low-endemic studies [17, 18, 20] and in two of the 12 high-endemic studies [23, 28]) and due to the general absence of reporting information about 'lack of allocation concealment' (all studies) and 'lack of blinding' (of the persons who analysed the blood slides) (15 of the 16 studies) (see Table S3 for further details). Therefore, the level of evidence was downgraded from high to moderate. Meta-analyses demonstrated that the results could be considered as precise (total number of malaria cases >300 and/or statistical significant effect around the pooled estimate). Although meta-analyses showed heterogeneity of the results, the level of evidence was not further downgraded for inconsistency because the majority of studies were in favour of the TNs (14 of the 15 studies) or the untreated nets (eight of the 14 studies). No indirectness was addressed as all studies included the study population of interest and only direct malaria-related outcomes (i.e. parasite prevalence and parasite incidence) were extracted.

Publication bias could not be assessed in low-endemic area studies due to the limited number of studies. Visual inspection could suspect publication bias in the high-endemic studies [five outliers in the funnel plot TNs *vs.* NNs (Figure S1), three outliers in the funnel plot UNs *vs.* NNs (Figure S2)]. However, no evidence of publication bias was found based on the Egger's test ($P = 0.17$ for TNs *vs.* NNs, $P = 0.05$ for UNs no NNs). All together, the strength of the body of evidence for both the low- and high-endemic areas can be considered as moderate.

Synthesis of study findings

As Table S4 shows, we observed no significant differences ($P < 0.05$) or substantial heterogeneity (I^2 ranged from 0% to 41%, see Tables 1 and 2) between types of study design (clustered randomised controlled trials *vs.* controlled interrupted time series) and duration of the impregnation period (<1 year *vs.* ≥1 year). On the

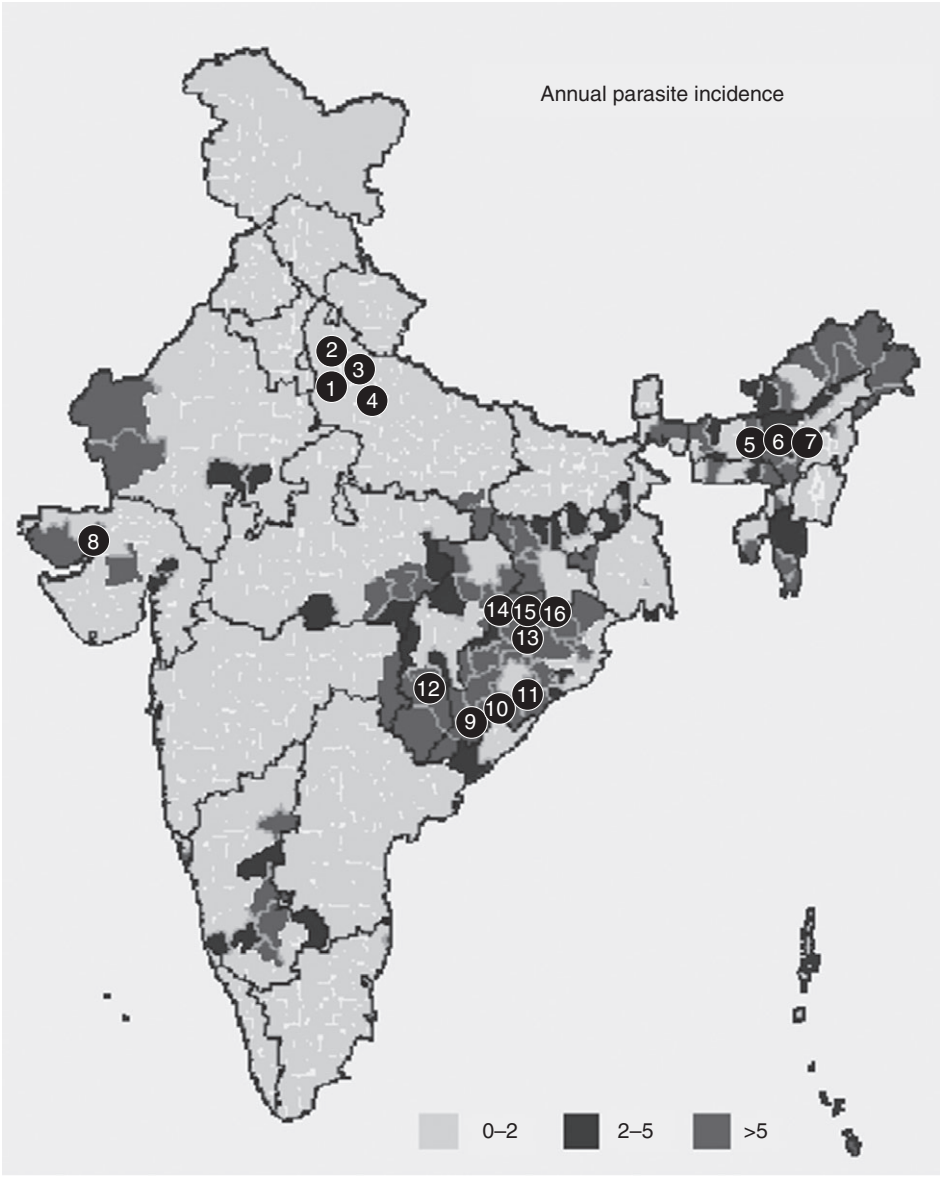

Figure 2 Classification of included studies into low-endemic *vs.* high-endemic areas, based on the annual parasite incidence. Figure was adapted from 'Estimation of True Malaria Burden in India' [42].

contrary, moderate heterogeneity in results was present between low-endemic areas and high-endemic areas (i.e. $I^2 = 49\%$, Figure 3). These findings support our decision to separate the analysis for type of study location (low endemic *vs.* high endemic) and pooling the data from different study designs.

An overlap was observed between the pooled risk ratios (and 95% CI) based on random-effects models and fixed-effects models. Hence, we opted to report the more conservative results (i.e. broader 95% confidence intervals) of the random-effects models (Table 3).

TNs *vs.* NNs

By pooling the data (Figure 3), parasite prevalence was found to be 0.25% (14/5533, low-endemic area) and 4.3% (2031/46662, high-endemic area) in the TN group compared to 2% (105/5257, low-endemic area) and

Table 1 Subgroup analysis: clustered randomised controlled trials *vs.* interrupted controlled time series

	Clustered randomized controlled trials [pooled RR (95% CI)]	Controlled interrupted time series [pooled RR (95% CI)]	*P*-value (chi-square test as test for subgroup differences)	Overall I^2 (%) (for subgroup differences)
Treated *vs.* no nets				
Low-endemic area	0.32 (0.13, 0.81)	0.12 (0.04, 0.39)	0.19	41
High-endemic area	0.37 (0.27, 0.49)	0.29 (0.20, 0.44)	0.38	0
Untreated *vs.* no nets				
Low-endemic area	0.36 (0.16, 0.81)	0.55 (0.26, 1.17)	0.46	0
High-endemic area	0.74 (0.58, 0.94)	0.63 (0.39, 1.01)	0.55	0

Table 2 Subgroup analysis: intervention period <1 year *vs.* intervention period ≥1 year

	Impregnation period <1 year [pooled RR (95% CI)]	Impregnation period ≥1 year [pooled RR (95% CI)]	*P*-value (chi-square test as test for subgroup differences)	Overall I^2 (%) (for subgroup differences)
Treated *vs.* no nets				
High-endemic area	0.21 (0.13, 0.33)	0.34 (0.19, 0.61)	0.21	36
Untreated *vs.* no nets				
High-endemic area	0.74 (0.53, 1.02)	0.67 (0.52, 0.86)	0.63	0

9.5% (4276/45070, high-endemic area) in the NN group. A statistical significant reduced risk of parasite prevalence was found in high-endemic areas [66% risk reduction, overall RR 0.34 (95% CI; 0.25, 0.45), $P < 0.00001$], and this observation was even more pronounced in the low-endemic areas [84% risk reduction, overall RR 0.16 (95% CI; 0.06, 0.44), $P < 0.0001$]. The parasite incidence rates per 1000 population per year were two (low-endemic area) and 81 (high-endemic area) in the TN group *vs.* 13 (low-endemic area) and 190 (high-endemic area) in the NN group, with and incidence rate ratio of 0.20 [(95% CI; 0.10, 0.39), $P < 0.05$] and 0.35 [(95% CI; 0.26, 0.48), $P < 0.05$] for low- and high-endemic areas, respectively.

UNs *vs.* NNs

By pooling the data, the parasite prevalence was found to be 0.8% (51/6115, low-endemic area) and 8.3% (1328/15963, high-endemic area) in the UNs group compared to 1.9% (105/5257, low-endemic area) and 12% (1720/14423, high-endemic area) in the NNs group. A statistical significant reduced risk of parasite prevalence was found in high-endemic areas [30% risk reduction, overall RR 0.70 (95% CI; 0.56, 0.87), $P < 0.00001$], which was also more pronounced (cf. TNs) in the low-endemic areas [51% risk reduction, overall RR 0.49 (95% CI; 0.28, 0.84), $P = 0.01$]. The average absolute gain in risk reduction on parasite prevalence when using TNs instead of using UNs is approximately 30% (81% *vs.* 51% in low-endemic areas and 66% *vs.* 30% in high-endemic areas). The parasite incidence rates per 1000 population per year were five (low-endemic area) and 148 (high-endemic area) in the TNs group compared to 15 (low-endemic area) and 202 (high-endemic area) in the NNs group, with a parasite incidence rate ratio of 0.38 [(95% CI; 0.23, 0.62), $P < 0.05$] and 0.77 [(95% CI; 0.62, 0.95), $P < 0.05$] for low- and high-endemic areas, respectively.

TNs were significantly more effective than UNs in the prevention of malaria in both low-endemic [68% risk reduction, pooled RR 0.32 (95% CI; 0.13, 0.78)] and high-endemic areas [56% risk reduction, pooled RR 0.44 (95% CI; 0.30, 0.66)].

No significant differences were observed when comparing long-lasting insecticidal nets *vs.* conventionally treated nets [low-endemic area: pooled RR 0.12 (95% CI; 0.02, 0.98) *vs.* pooled RR 0.21 (0.08, 0.57), $P = 0.64$; high-endemic area: pooled RR 0.23 (95% CI; 0.13, 0.39) *vs.* pooled RR 0.35 (0.25, 0.5), $P = 0.18$].

Regarding results within the low-/high-endemic areas, there was evidence of heterogeneity across all analyses [$P \leq 0.05$ in chi-square tests, I^2 ranged from 55% (Figure 3) to 95% (Figure 4)], which was not explained by the study location (low- *vs.* high-endemic area).

The study that was not included in the meta-analysis (no raw data published) found that TNs or UNs had a significant effect on malaria (monthly parasite index) compared to no nets.

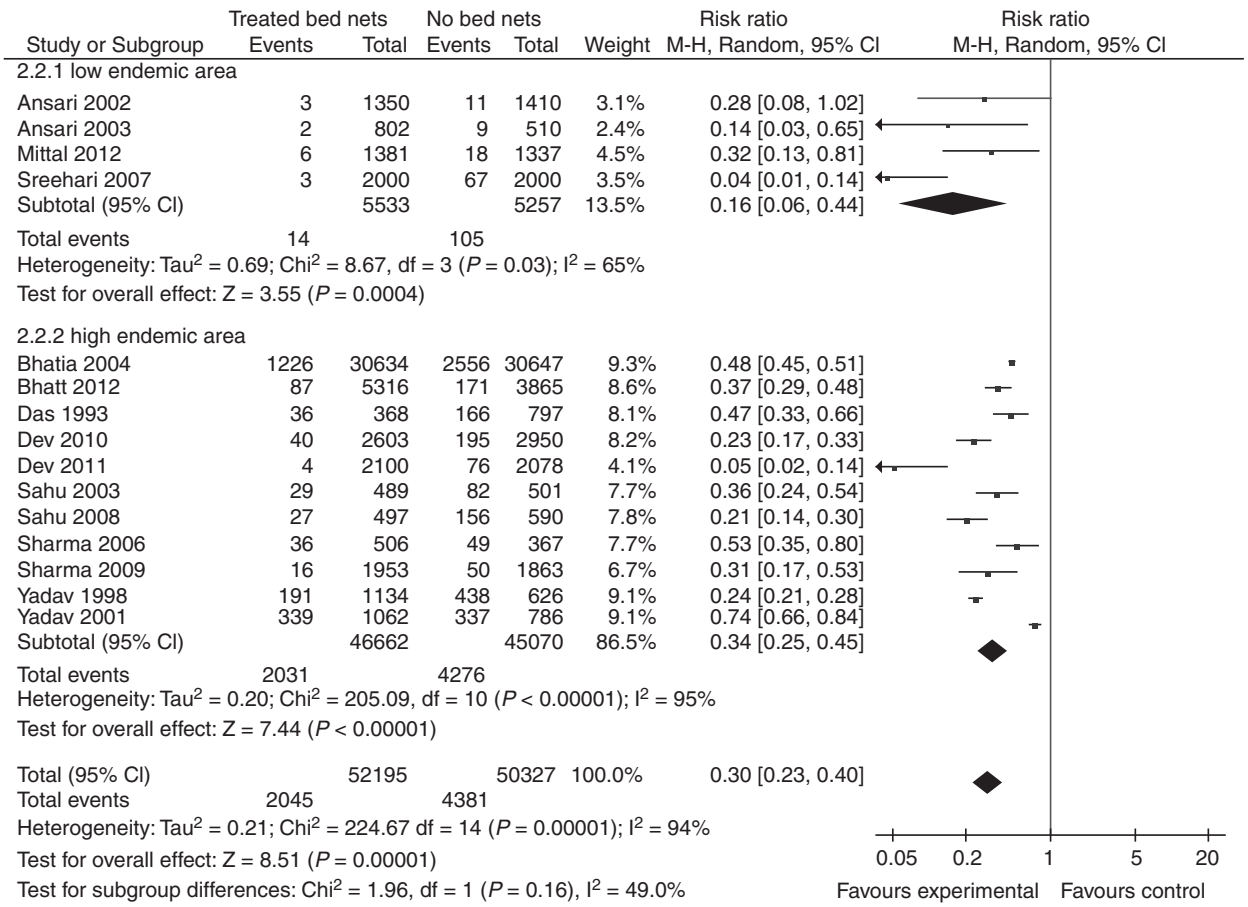

Figure 3 Study-specific risk ratios for the presence of parasites in the blood (parasite prevalence) between insecticide-treated nets and no nets. Each dot represents the risk ratio of the respective study together with a 95% confidence interval (CI). The size of the box represents the weight of the study in the meta-analysis. Weights are from random-effects analysis.

Table 3 Pooled risk ratios (with 95% CI) based on random-effects model *vs.* fixed-effects model

	Random-effects model [pooled RR (95% CI)]	Fixed-effects model [pooled RR (95% CI)]
Treated *vs.* no nets		
Low-endemic area	0.16 (0.06, 0.44)	0.13 (0.07, 0.22)
High-endemic area	0.34 (0.25,0.45)	0.44 (0.42,0.46)
Untreated *vs.* no nets		
Low-endemic area	0.49 (0.28, 0.84)	0.42 (0.30, 0.60)
High-endemic area	0.70 (0.56, 0.87)	0.63 (0.59, 0.67)

Discussion

The present systematic review shows that the use of TNs or UNs is both effective interventions for malaria prevention in India, whether living in low-endemic or high-endemic areas. Furthermore, TNs are more effective than UNs (approximately 30% more risk reduction).

Since 1953, the Government of India (Ministry of Health and Family Welfare) organises the National Vector-Borne Disease Program, which is an umbrella for prevention and control of 6 vectorborne diseases: malaria, dengue, chikungunya, Japanese encephalitis, kala-azar and filariasis. This programme includes both an annual IRS (DDT and malathion) in high-endemic areas and the widespread use of bed nets. The present study shows that TN and UN both are effective interventions to control malaria, in both low- and high-endemic areas, and might be preferable to IRS as TNs provide better protection against any infection (*Plasmodium falciparum* or *Plasmodium vivax*) than IRS in India (risk ratio IRS:TN = 1.70) [33]. Despite the proven effectiveness of net usage in

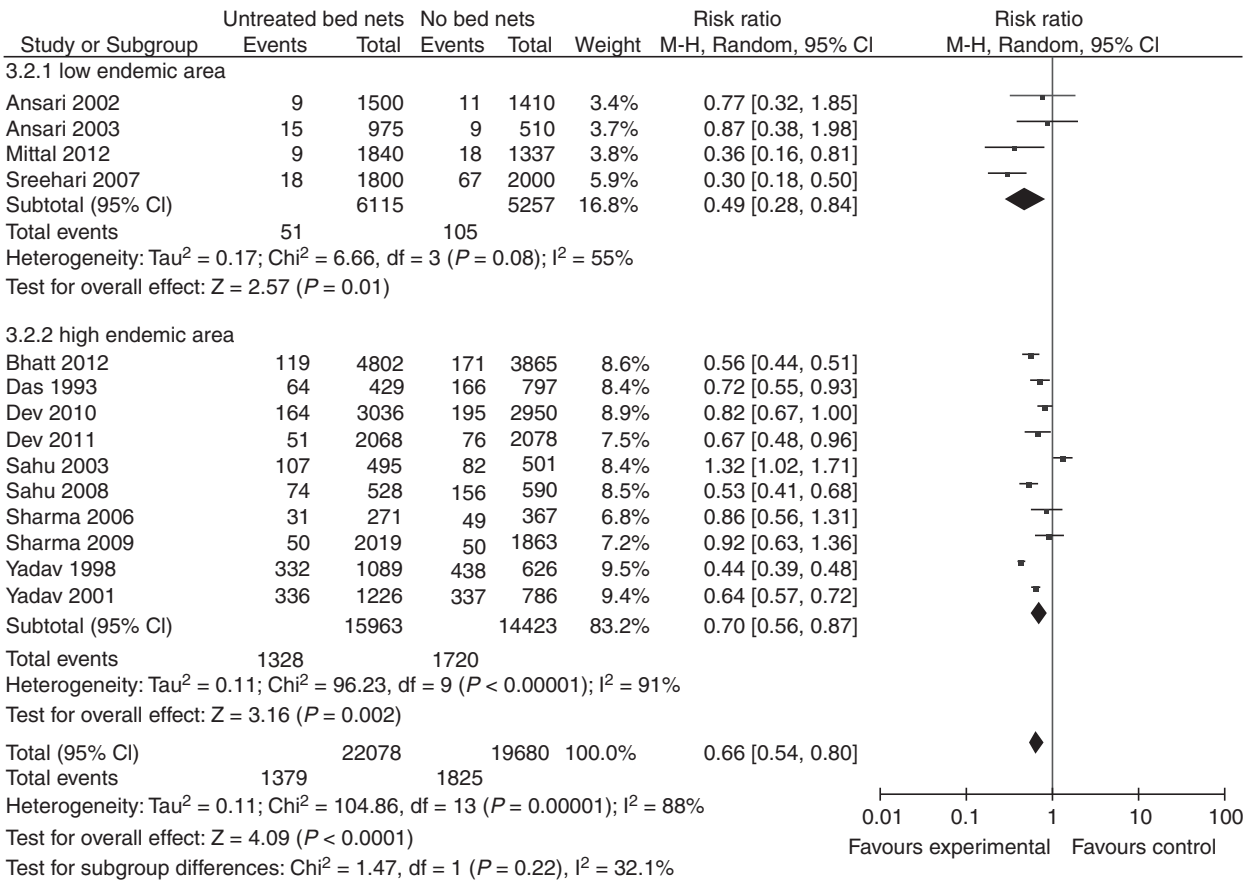

Figure 4 Study-specific risk ratios for the presence of parasites in the blood (parasite prevalence) between untreated nets and no nets. Each dot represents the risk ratio of the respective study together with a 95% confidence interval (CI), and the size of the box represents the weight of the study in the meta-analysis. Weights are from random-effects analysis.

India by our meta-analyses, the transmission of malaria remains complex, especially in high-endemic areas, due to factors such as variation in vast terrain, population, practices, ecological conditions and multiplicity of disease vectors [9, 10].

To our knowledge, this is the first study that systematically reviewed all available evidence from Indian studies on the effectiveness of TN and UN in the prevention of malaria. In 2004, a Cochrane systematic review already showed that TNs were highly effective in reducing morbidity and child mortality from malaria. This review also clearly showed that TNs have an average risk reduction effect on parasite prevalence of 13–42% (RR 0.58–0.87), which is even higher in our analysis (65–84% risk reduction). Only non-Indian randomised trials were included in the Cochrane review because Indian randomised trials were published after January 2003 (i.e. end date of search strategy in the Cochrane review) [19, 21, 22, 24–27, 31], with the exception of the study by Yadav *et al.*, published in 2001 [29]. The latter study was not marked as a clustered randomised controlled trial in the Cochrane review because the unit of allocation in all included Indian clustered randomised trials consisted of a set of different villages, which were pooled before randomising into the intervention or control group. On the contrary, clustered randomised controlled trials in the Cochrane review were set up more rigorously by pairing villages according to size, geographic location, malaria incidence at baseline, etc. after which randomisation took place. The inaccurate randomisation process in the Indian trials, together with the absence of information on allocation concealment and/or blinding and the absence of randomisation in the controlled interrupted time series resulted in downgrading the level of evidence from high to moderate (due to limitations in study design).

By calculating both risk ratios (from parasite prevalence) and rate ratios (from annual parasite incidence), we were able to state that the probability of having

parasites in the blood is less when TNs and UNs have been used [risk ratio (95% CI) below one] compared to NNs. Secondly, the rate ratios (95% CI) below one (intervention *vs*. control) indicated that TNs and UNs are probably causally associated with the prevention of parasites in the blood. As mentioned, the protective effect of TNs was more pronounced compared to UNs.

A minimal but no maximal target impregnation dose (depending on the insecticide) was used as an inclusion criterion for the intervention (i.e. TNs). Hence, we included both conventionally treated nets (effective during one year without retreatment) and long-lasting treated nets (effective during three years without retreatment) [34]. We assume that this difference in effect would not have an impact on our results as the post-intervention period (i.e. time until the first re-impregnation period) was ≤1 year in the majority of the studies (15/17). This was confirmed by observing no statistically significant differences between conventionally treated nets and long-lasting treated nets (subgroup analysis).

This review is part of a collaboration between Belgian Red Cross-Flanders and the Indian Red Cross Society to develop evidence-based Indian first aid and prevention guidelines. Besides collecting the best available scientific evidence, gathering information from experts in the field of malaria and taking into account the preferences of the target population (Indian laypeople) are essential when developing evidence-based guidelines.

From the perspective of Indian laypeople (target population), treated or untreated nets have four major advantages over indoor residual spraying. Firstly, nets can work in most of the rural areas including inaccessible areas inhabited by ethnic tribes. Secondly, nets are easily portable by migrating populations during natural calamities such as droughts, flash floods, cyclones, avalanches or landslides. Thirdly, TNs could be seen as the preferred intervention due to the minimal amount (~5%) of adverse health events (skin irritation, eye irritation) and the possible collateral benefits (i.e. relief from other household pests such as head lice, bed bugs, cockroaches, ants and houseflies) [19, 25, 31, 32]. Fourthly, a randomised cluster trial in India found that net usage is a more cost-effective intervention than IRS by showing a significant lower mean cost per malaria case averted (US$2 *for treated nets versus US$7* for IRS) [21]. A possible disadvantage is that protection is only offered during sleeping time and that nets may be disused or not used by a proportion of the population. However, it has been shown that more users are favouring the use of insecticide-treated nets (compliance rate 55–90%) [19, 27, 31, 35] over the conventional indoor residual spraying (refusal rate 70–80%) [36, 37]. Hence, proper health education is needed to increase knowledge, attitude and practices at the individual and community level to enhance IRS coverage and net usage for successful malaria control. Special attention for this education has to be given to the high-endemic areas (north-eastern states) because these areas are the most vulnerable to climate change (i.e. an extended transmission window) [38].

Despite the rapid decline in malaria incidence over the last decades [1], malaria is not completely eliminated (yet) in India. Therefore, high-risk populations, that is people living in the most severely affected areas with poor healthcare access, should be targeted in future research projects. Interventions including the distribution of bed nets by non-governmental organisations local to the endemic area, mobile malaria clinics, the use of mobile technology [9], the use of a malaria vaccine [39], and/or greater engagement of village-level health workers for early diagnosis and treatment [40] could be promising for the further reduction and elimination of malaria in India. Besides these future research projects, the implementation of innovative (effective) vector control interventions should be facilitated by the central and state governments. Unfortunately, the available resources/funds are limited the last years (due to the financial crisis worldwide), which makes this implementation challenging [41].

In summary, we can conclude that using insecticide-treated nets or untreated nets (to a significant lesser extent) is both effective malaria prevention techniques for low- and high-endemic areas in India. It was shown that the magnitude of the average effect was higher in the Indian studies compared to the non-Indian studies (as analysed by the Cochrane Review) [8]. These findings were based on 16 experimental studies of moderate quality and support the use of insecticide-treated nets by the National Vector-Borne Disease Program of India.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Details of the search strategy terms in the different databases.

Figure S1. Funnel plot representing the studies (insecticide-treated nets *vs.* no nets) performed in high endemic areas (diamonds). The outer dashed lines indicate the triangular region in which 95% of the studies are expected. The vertical dotted line shows the average risk ratio across all trials.

Figure S2. Funnel plot representing the studies (untreated nets *vs.* no nets) performed in high endemic areas (diamonds). The outer dashed lines indicate the triangular region in which 95% of the studies are expected. The vertical dotted line shows the average risk ratio across all trials.

Table S1. The 27-item PRISMA checklist

Table S2. Summary of the study characteristics

Table S3. Limitations in study design

Table S4. Summary of study findings included in the meta-analyses

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