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TABLE OF CONTENTS

HEADER . . . 1
ABSTRACT . . . 1
PLAIN LANGUAGE SUMMARY . . . 2
SUMMARY OF FINDINGS FOR THE MAIN COMPARISON . . . 4
BACKGROUND . . . 7
OBJECTIVES . . . 7
METHODS . . . 7
Figure 1. . . . 9
RESULTS . . . 11
Figure 2. . . . 13
ADDITIONAL SUMMARY OF FINDINGS . . . 16
DISCUSSION . . . 21
AUTHORS' CONCLUSIONS . . . 22
ACKNOWLEDGEMENTS . . . 22
REFERENCES . . . 22
CHARACTERISTICS OF STUDIES . . . 26
DATA AND ANALYSES . . . 64
Analysis 1.1. Comparison 1 Insecticide-treated nets versus no nets, Outcome 1 Child mortality from all causes. . . . 65
Analysis 1.2. Comparison 1 Insecticide-treated nets versus no nets, Outcome 2 P falciparum uncomplicated episodes. 66
Analysis 1.3. Comparison 1 Insecticide-treated nets versus no nets, Outcome 3 P falciparum uncomplicated episodes (cumulative incidence). . . . 67
Analysis 1.4. Comparison 1 Insecticide-treated nets versus no nets, Outcome 4 P vivax uncomplicated episodes (cumulative incidence). . . . 67
Analysis 1.5. Comparison 1 Insecticide-treated nets versus no nets, Outcome 5 Any Plasmodium spp. uncomplicated episodes. . . . 68
Analysis 1.6. Comparison 1 Insecticide-treated nets versus no nets, Outcome 6 P falciparum prevalence. . . . 68
Analysis 1.7. Comparison 1 Insecticide-treated nets versus no nets, Outcome 7 P vivax prevalence. . . . 69
Analysis 1.8. Comparison 1 Insecticide-treated nets versus no nets, Outcome 8 Severe malaria episodes. . . . 70
Analysis 1.9. Comparison 1 Insecticide-treated nets versus no nets, Outcome 9 Anaemia (mean packed cell volume). 70
Analysis 2.1. Comparison 2 Insecticide-treated nets versus untreated nets, Outcome 1 Child mortality from all causes. 71
Analysis 2.2. Comparison 2 Insecticide-treated nets versus untreated nets, Outcome 2 P falciparum uncomplicated episodes. . . . 72
Analysis 2.3. Comparison 2 Insecticide-treated nets versus untreated nets, Outcome 3 P vivax uncomplicated episodes. 73
Analysis 2.4. Comparison 2 Insecticide-treated nets versus untreated nets, Outcome 4 P vivax uncomplicated episodes (cumulative incidence). . . . 73
Analysis 2.5. Comparison 2 Insecticide-treated nets versus untreated nets, Outcome 5 Any Plasmodium spp. uncomplicated episodes (cumulative incidence). . . . 74
Analysis 2.6. Comparison 2 Insecticide-treated nets versus untreated nets, Outcome 6 P falciparum prevalence. . . . 75
Analysis 2.7. Comparison 2 Insecticide-treated nets versus untreated nets, Outcome 7 P vivax prevalence. . . . 75
Analysis 2.8. Comparison 2 Insecticide-treated nets versus untreated nets, Outcome 8 Any Plasmodium spp. prevalence. 76
Analysis 2.9. Comparison 2 Insecticide-treated nets versus untreated nets, Outcome 9 Anaemia (mean packed cell volume). . . . 76
APPENDICES . . . 76
WHAT'S NEW . . . 79
HISTORY . . . 80
CONTRIBUTIONS OF AUTHORS . . . 81
DECLARATIONS OF INTEREST . . . 81
SOURCES OF SUPPORT . . . 81
DIFFERENCES BETWEEN PROTOCOL AND REVIEW . . . 82
INDEX TERMS . . . 82

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[Intervention Review]

Insecticide-treated nets for preventing malaria

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ABSTRACT

Background

A previous version of this Cochrane Review identified that insecticide-treated nets (ITNs) are effective at reducing child mortality, parasite prevalence, and uncomplicated and severe malaria episodes. Insecticide-treated nets have since become a core intervention for malaria control and have contributed greatly to the dramatic decline in disease incidence and malaria-related deaths seen since the turn of the millennium. However, this time period has also seen a rise in resistance to pyrethroids (the insecticide used in ITNs), raising questions over whether the evidence from trials conducted before resistance became widespread can be applied to estimate the impact of ITNs on malaria transmission today.

Objectives

The primary objective of this review was to assess the impact of ITNs on mortality and malaria morbidity, incorporating any evidence published since the previous update into new and existing analyses, and assessing the certainty of the resulting evidence using GRADE.

Search methods

We searched the Cochrane Infectious Diseases Group Specialized Register, the Cochrane Central Register of Controlled Trials (CENTRAL) published in the Cochrane Library, MEDLINE, Embase, LILACS, the World Health Organization (WHO) International Clinical Trials Registry Platform, ClinicalTrials.gov, and the ISRCTN registry for new trials published since 2004 and up to 18 April 2018.

Selection criteria

We included individual randomized controlled trials (RCTs) and cluster RCTs comparing bed nets or curtains treated with a synthetic pyrethroid insecticide at a minimum target impregnation dose recommended by the WHO with no nets or untreated nets.

Data collection and analysis

One review author assessed the identified trials for eligibility and risk of bias, and extracted data. We compared intervention and control data using risk ratios (RRs), rate ratios, and mean differences, and presented all results with their associated 95% confidence intervals (CIs). We assessed the certainty of evidence using the GRADE approach. We drew on evidence from a meta-analysis of entomological outcomes stratified by insecticide resistance from 2014 to inform the GRADE assessments.

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Main results

Our updated search identified three new trials. A total of 23 trials met the inclusion criteria, enrolling more than 275,793 adults and children. The included studies were conducted between 1987 and 2001.

ITN versus no nets

Insecticide-treated nets reduce child mortality from all causes by 17% compared to no nets (rate ratio 0.83, 95% CI 0.77 to 0.89; 5 trials, 200,833 participants, high-certainty evidence). This corresponds to a saving of 5.6 lives (95% CI 3.6 to 7.6) each year for every 1000 children protected with ITNs. Insecticide-treated nets also reduce the incidence of uncomplicated episodes of *Plasmodium falciparum* malaria by almost a half (rate ratio 0.55, 95% CI 0.48 to 0.64; 5 trials, 35,551 participants, high-certainty evidence) and probably reduce the incidence of uncomplicated episodes of *Plasmodium vivax* malaria (risk ratio (RR) 0.61, 95% CI 0.48 to 0.77; 2 trials, 10,967 participants, moderate-certainty evidence).

Insecticide-treated nets were also shown to reduce the prevalence of *P falciparum* malaria by 17% compared to no nets (RR 0.83, 95% CI 0.71 to 0.98; 6 trials, 18,809 participants, high-certainty evidence) but may have little or no effect on the prevalence of *P vivax* malaria (RR 1.00, 95% CI 0.75 to 1.34; 2 trials, 10,967 participants, low-certainty evidence). A 44% reduction in the incidence of severe malaria episodes was seen in the ITN group (rate ratio 0.56, 95% CI 0.38 to 0.82; 2 trials, 31,173 participants, high-certainty evidence), as well as an increase in mean haemoglobin (expressed as mean packed cell volume) compared to the no-net group (mean difference 1.29, 95% CI 0.42 to 2.16; 5 trials, 11,489 participants, high-certainty evidence).

ITN versus untreated nets

Insecticide-treated nets probably reduce child mortality from all causes by a third compared to untreated nets (rate ratio 0.67, 95% CI 0.36 to 1.23; 2 trials, 25,389 participants, moderate-certainty evidence). This corresponds to a saving of 3.5 lives (95% CI -2.4 to 6.8) each year for every 1000 children protected with ITNs. Insecticide-treated nets also reduce the incidence of uncomplicated *P falciparum* malaria episodes (rate ratio 0.58, 95% CI 0.44 to 0.78; 5 trials, 2036 participants, high-certainty evidence) and may also reduce the incidence of uncomplicated *P vixax* malaria episodes (rate ratio 0.73, 95% CI 0.51 to 1.05; 3 trials, 1535 participants, low-certainty evidence).

Use of an ITN probably reduces *P falciparum* prevalence by one-tenth in comparison to use of untreated nets (RR 0.91, 95% CI 0.78 to 1.05; 3 trials, 2,259 participants, moderate-certainty evidence). However, based on the current evidence it is unclear whether or not ITNs impact on *P vivax* prevalence (1 trial, 350 participants, very low certainty evidence) or mean packed cell volume (2 trials, 1,909 participants, low certainty evidence).

Authors' conclusions

Although there is some evidence that insecticide resistance frequency has some effects on mosquito mortality, it is unclear how quantitatively important this is. It appeared insufficient to downgrade the strong evidence of benefit on mortality and malaria illness from the trials conducted earlier

PLAIN LANGUAGE SUMMARY

Insecticide-treated nets for preventing malaria

What is the aim of this review?

Insecticide-treated nets (ITNs) are a core intervention for malaria control. A previous version of this Cochrane Review showed they are very effective at reducing malaria-related death and illness. Since the review was published, many areas affected by malaria have reported mosquito populations that are resistant to the insecticides used in ITNs. The aim of this review update was to evaluate the available evidence and find out whether ITNs continue to be effective at controlling the disease. Cochrane researchers collected and analysed relevant studies and assessed the overall certainty of the evidence.

What was studied in the review?

This review update summarized trials published since the previous review that evaluated the impact of ITNs on malaria-related deaths and illness, compared to both no nets and untreated nets. After searching for relevant trials up to 18 April 2018, we identified three new randomized controlled trials (studies in which participants are assigned to a treatment group using a random method). In total, we

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included 23 trials, enrolling more than 275,000 adults and children, to evaluate the effectiveness of ITNs for reducing the burden of malaria. The included studies provided evidence of the impact of ITNs on infection from two types of malaria parasites, *Plasmodium falciparum* and *Plasmodium vivax*.

What are the main results of the review?

Twelve trials (nine in Africa, one in Cambodia, one in Myanmar, and one in Pakistan) assessed the impact of ITNs in comparison to no nets. From these trials, we concluded that ITNs reduce the child mortality from all causes, corresponding to a saving of 5.6 lives each year for every 1000 children protected with ITNs (high-certainty evidence). ITNs also reduce the number of *P falciparum* cases per person per year and the proportion of people infected with *P falciparum* parasites (high-certainty evidence). ITNs probably reduce the number of *P vivax* cases per person per year and may reduce the proportion of people infected with *P vivax* parasites (moderate-certainty evidence).

Eleven trials (three in sub-Saharan Africa, six in Latin America, and two in Thailand) assessed the impact of ITNs in comparison to untreated nets. From these trials, we concluded that ITNs probably reduce the child mortality from all causes, corresponding to a saving of 3.5 lives each year for every 1000 children protected with ITNs (moderate-certainty evidence). ITNs also reduce the number of *P falciparum* cases per person per year (high-certainty evidence), and probably reduce the proportion of people infected with *P falciparum* parasites (moderate-certainty evidence). Whilst ITNs may also reduce the number of *P vivax* cases per person per year (low-certainty evidence), it is unclear if the proportion of people infected with *P vivax* parasites is any lower in those using an ITN than those using an untreated net (very low certainty evidence).

In interpreting these results, we considered that there are a growing number of mosquito populations that have been shown to be able to survive exposure to the insecticides used in ITNs. However, it is currently unclear how quantitatively important this is, and this seems insufficient to downgrade the existing evidence of an effect of ITNs in preventing malaria-related mortality and illness.

Key messages

ITNs, whether compared to no nets or to untreated nets, continue to be effective at reducing child mortality and malaria-related illness in affected areas.

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SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Insecticide-treated bed nets and curtains (ITNs) compared to no nets for preventing malaria

Patient or population: people of all ages living in malaria transmission settings
Setting: Burkina Faso 1996 (Halbluetzel 1996); Cameroon 1992 (Moyou-Somo 1995); Cambodia 2002 (Sochantha 2006); Ghana 1995 (Binka 1996); Ivory Coast 2000 (Henry 2005); Kenya 1988 (Sexton 1990); Kenya 1995 (Nevill 1996) and 1998 (Phillips-Howard 2003); Myanmar 1999 (Smithuis 2013); Sierra Leone 1993 (Marbiah 1998); Pakistan 1991 (Rowland 1996); Tanzania 1996 (Fraser-Hurt 1999)
Intervention: ITNs
Comparison: no nets

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Risk with no nets	Risk with ITNs				
Child mortality from all causes	Children of all ages		Rate ratio 0.83 (0.77 to 0.89)	200,833 (5 RCTs)	⊕⊕⊕⊕ HIGH[a]	Insecticide-treated bed nets and curtains reduce all-cause child mortality compared to no nets
	32.9 per 1000	27.3 per 1000 (25.3 to 29.3)				
	Children aged 1 to 59 months					
	37.8 per 1000	31.4 per 1000 (29.1 to 33.6)				
Plasmodium falciparum uncomplicated episodes[g]	178 per 1000	96 per 1000 (86 to 107)	Rate ratio 0.55 (0.48 to 0.64)	35,551 (5 RCTs)	⊕⊕⊕⊕ HIGH[a]	Insecticide-treated bed nets and curtains reduce the incidence of uncomplicated episodes of *P falciparum* malaria compared to no nets.

Plasmodium vivax uncomplicated episodes (cumulative incidence)	149 per 1000	91 per 1000 (71 to 114)	Risk ratio 0.61 (0.48 to 0.77)	10,967 (2 RCTs)	⊕⊕⊕◯ MODERATE[a,b] *due to indirectness*	Insecticide-treated bed nets and curtains probably reduce the incidence of uncomplicated episodes of *P vivax* malaria compared to no nets.
Any *Plasmodium* spp. uncomplicated episodes	256 per 1000	128 per 1000 (72 to 231)	Rate ratio 0.50 (0.28 to 0.90)	8,395 (1 RCT)	⊕⊕◯◯ LOW[a,c,d] *due to indirectness*	Insecticide-treated bed nets and curtains may reduce the incidence of uncomplicated episodes of any *Plasmodium* species compared to no nets.
P falciparum prevalence	147 per 1000	122 per 1000 (102 to 144)	Risk ratio 0.83 (0.71 to 0.98)	18,809 (6 RCTs)	⊕⊕⊕⊕ HIGH[a]	Insecticide-treated bed nets and curtains reduce the prevalence of *P falciparum* malaria compared to no nets.
P vivax prevalence	130 per 1000	130 per 1000 (98 to 175)	Risk ratio 1.00 (0.75 to 1.34)	10,967 (2 RCTs)	⊕⊕◯◯ LOW[a,b,e] *due to indirectness and imprecision*	Insecticide-treated bed nets and curtains may have little or no effect on the prevalence of *P vivax* malaria compared to no nets.
Severe malaria episodes	15.1 per 1000	8.5 per 1000 (5.7 to 12.4)	Rate ratio 0.56 (0.38 to 0.82)	31,173 (2 RCTs)	⊕⊕⊕⊕ HIGH[a]	Insecticide-treated bed nets and curtains reduce the incidence of severe malaria episodes compared to no nets

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Anaemia (mean packed cell volume)	31.4	32.7 (31.8 to 33.6)	Mean difference 1.29 (0.42 to 2.16)	11,489 (5 RCTs)	⊕⊕⊕⊕ HIGH[a,f]	Insecticide-treated bed nets and curtains increase the mean packed cell volume compared to no nets

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
Abbreviations: CI: confidence interval; **RCT:** randomized controlled trial; **ITN**: Insecticide-treated net

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a]Not downgraded for indirectness: for most included studies, it is unclear whether insecticide resistance was present. The review authors judge that there is not convincing evidence that insecticide resistance would reduce the impact of ITNs on the included epidemiological outcomes. A previous review that included entomological outcomes showed the difference in mosquito mortality risk using ITNs compared with untreated nets modestly decreased as insecticide resistance increased (Strode 2014). However, mosquito mortality risk remained significantly higher for ITNs than for untreated nets, regardless of the resistance status.

[b]Downgraded one level for indirectness: most data are provided by a trial in two refugee camps in Pakistan. The second trial is in Myanmar and provides data only for children younger than 10 years. It is not clear how confidently the information can be applied to other populations.

[c]Not downgraded for imprecision: the smallest effect size is still a sizable a reduction of 56 episodes per 1000 child-years.

[d]Downgraded two levels for indirectness: the evidence comes from one trial only, which was conducted in Myanmar, and in which participants were exclusively children aged younger than 10 years. It is not clear how confidently the information can be applied to other populations.

[e]Downgraded one level for imprecision: the confidence interval includes both a sizable increase and decrease in prevalence.

[f]Not downgraded for inconsistency: although the I^2 of 69% indicated substantial heterogeneity, ITNs showed an increase in mean packed cell volume universally across each of the five trials.

[g]The cumulative incidence of *P falciparum* clinical episodes was also reported (Analysis 1.3: RR 0.44, 95% CI 0.31 to 0.62; moderate-certainty evidence). As this is consistent with the effect on the incidence rate, we did not present both results in the 'Summary of findings' table.

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BACKGROUND

The 2004 Cochrane Review 'Insecticide-treated bed nets and curtains for preventing malaria' demonstrated the effectiveness of insecticide-treated nets (ITNs) for reducing malaria prevalence, morbidity, and mortality. Incorporating information from 22 randomized controlled trials (RCTs), the review found that ITNs reduced child mortality by 17%. In areas of stable malaria transmission, ITNs also reduced parasite prevalence by 13%, uncomplicated malaria episodes by 50%, and severe malaria by 45% compared to equivalent populations with no nets (Lengeler 2004). The World Health Organization (WHO) now recommends ITNs as a core intervention for malaria control.

Between 2010 and 2015, the estimated percentage of the at-risk population sleeping under an ITN rose from 30% to 53%. During this time, disease incidence and malaria-related deaths have fallen by 21% and 29%, respectively (WHO 2016). Additionally, parasite prevalence in endemic sub-Saharan Africa decreased by 50% between 2001 and 2015, with 68% of this decline attributed to the use of ITNs (Bhatt 2015)

Emerging insecticide resistance poses a challenge to current malaria vector control methods. There are only four classes of insecticide in use for public health, with just two mechanisms of action. A lack of funding for research into new insecticides has meant that the most recently developed class is the pyrethroids, which were developed over 40 years ago (Ranson 2011). During this period, 27 countries have reported resistance to pyrethroids, and the number of susceptible *Anopheles* populations continues to decline (Ranson 2016). The effectiveness of ITNs is particularly at risk, as pyrethroids are the only class of insecticide considered safe for prolonged human contact and therefore appropriate for ITN use (Zaim 2000).

Insecticide resistance is commonly detected using laboratory-based bioassays and experimental hut studies, but these do not necessarily indicate reduced ITN impact on real-life clinical outcomes (Ranson 2016). It remains unclear whether the dramatic increases in ITN use and pyrethroid resistance in the years following Lengeler's 2004 review have reduced the clinical effectiveness of ITNs. The purpose of this review update was therefore to identify, critically appraise, and summarize any trials published since the last edition of the review, incorporating modern methods for systematic reviews that allow combined analysis of cluster RCTs (cRCTs), and assessment of the certainty of the estimates of the effect of ITNs. We were able to draw on a systematic review of entomological outcomes in the presence of pyrethroid resistance from 2014 to help inform the GRADE assessments for indirectness (Strode 2014).

OBJECTIVES

The primary objective of this review was to assess the impact of ITNs on mortality and malaria morbidity, incorporating any evidence published since the previous update into new and existing analyses, and assessing the certainty of the resulting evidence using GRADE.

METHODS

Criteria for considering studies for this review

Types of studies

Individual RCTs and cluster RCTs (cRCTs).

Types of participants

Children and adults living in malaria transmission settings.
We excluded trials examining only pregnant women, because these are reviewed elsewhere (Gamble 2006), and trials examining only soldiers or travellers, as these are not representative of the general population.

Types of interventions

Bed nets or curtains treated with a synthetic pyrethroid insecticide at a minimum target impregnation dose recommended by the WHO, which is as follows.

- 200 mg/m^2 permethrin or etofenprox.
- 30 mg/m^2 cyfluthrin.
- 20 mg/m^2 alpha-cypermethrin.
- 10 mg/m^2 deltamethrin/lambda-cyhalothrin.

No distinction was made between insecticide-treated bed nets and door/window/eave/wall curtains.
Control populations were those provided with either no net or with an untreated net.

Types of outcome measures

Primary outcomes

- Child mortality from all causes.

Secondary outcomes

- Uncomplicated clinical episodes: measured using site-specific definitions, including measured or reported fever, with or without parasitological confirmation. Measurements were usually done in the frame of prospective longitudinal studies, as a rate of episodes per unit of time (incidence). We also included trials using validated retrospective assessments in the frame of

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cross-sectional surveys, providing a percentage of the population who had experienced an uncomplicated episode in a unit of time (cumulative incidence). When reported separately, *P falciparum* and *P vivax* episodes were analysed separately. We also included trials that reported the incidence of episodes of any *Plasmodium* species.

- Parasite prevalence: parasite prevalence due to *P falciparum* and *P vivax* was obtained using the site-specific method for estimating parasitaemia, usually thick or thin blood smears or both. When more than one survey was done, the reported prevalence result is the average prevalence of all the surveys.
- Severe disease: measured using site-specific definitions, which were based on the WHO guidelines, WHO 1990, and on Marsh 1995. The definition included *P falciparum* parasitaemia. Cerebral malaria was defined as coma or prostration and/or multiple seizures. The cut-off for severe, life-threatening anaemia was set at 5.1 g/L (WHO 1990).
- Anaemia: expressed in mean packed cell volume (PCV), equivalent to the percentage haematocrit. Results given in grams per decilitre were converted with a standard factor of 3:1 so that 1 g/dL equals 3% PCV.
- The outcome measures below were considered in the previous review (Lengeler 2004), but were not considered priority outcomes at the time of this update and were therefore not included. Appendix 1 details the full inclusion criteria for this previous update.
    - High parasitaemia: measured using site-specific definitions of high parasitaemia, provided the cut-off value between high and low was determined prior to data analysis.
    - Splenomegaly: measured in all trials using the Hackett scale.
    - Anthropometric measures: standard anthropological measures (weight-for-age, height-for-age, weight-for-height, skinfold thickness, or mid-upper arm circumference)

Search methods for identification of studies

The previous review, Lengeler 2004, used the search strategy outlined below to identify included studies.

- The following databases were searched using the search terms and strategy described in Appendix 2: Cochrane Infectious Diseases Group Specialized Register (January 2003); Cochrane Central Register of Controlled Trials (CENTRAL), published in the Cochrane Library (Issue 1, 2003); MEDLINE (1966 to October 2003); Embase (1974 to November 2002); and LILACS (Latin American and Caribbean Health Science Information database) (1982 to January 2003).
- The following foreign language tropical medicine journals were handsearched, covering the period from 1980 to 1997: *Bulletin OCEAC*, *Bulletin de la Société de Pathologie Exotique*, *Médecine Tropicale*, and *Revista do Instituto de Medicina Tropical de Sao Paulo*.
- Researchers actively involved in the field of ITNs were contacted and asked about unpublished past or ongoing work.
- The following agencies, which have funded ITN trials, were contacted: UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR); International Development Research Centre (IDRC), Canada; the Department for International Development, UK; and the European Union Directorate-General XII.
- The following manufacturers of pyrethroids used for treating netting were contacted: AgrEvo (now part of Bayer), Bayer, Cyanamid, Mitsui, Sumitomo, and Zeneca (now part of Syngenta).
- The following reviews were consulted: Abdulla 1995; Bermejo 1992; Carnevale 1991; Cattani 1997; Choi 1995; Curtis 1992; Molyneaux 1994; Rozendaal 1989; Sexton 1994; Voorham 1997; WHO 1989; Xu 1988; Yadav 1997; and Zimmerman 1997.
- The following books on the subject of ITNs were consulted: *Control of Disease Vectors in the Community* (Curtis 1991), *Malaria: Waiting for the Vaccine* (Targett 1991), and *Net Gain, a New Method for Preventing Malaria Deaths* (Lengeler 1996).
- The reference lists of all trials identified by the above methods were consulted.

We considered for this review update all studies identified using the strategy above. Detailed below is the additional search process we undertook to identify new studies conducted since 2003.

Electronic searches

We searched the following databases, using the search terms and strategy described in Appendix 2: Cochrane Infectious Diseases Group Specialized Register (2003 to 18 April 2018); Cochrane Central Register of Controlled Trials (Issue 4, 2018); MEDLINE (PubMed, 2003 to 18 April 2018); Embase (Ovid, January 2003 to 18 April 2018); and LILACS (Latin American and Caribbean Health Science Information database) (2003 to 18 April 2018). To identify any ongoing trials, we also searched the World Health Organization (WHO) International Clinical Trials Registry Platform (www.who.int/ictrp/search/en/; 18 April 2018), ClinicalTrials.gov (https://clinicaltrials.gov/; 18 April 2018) and the ISRCTN registry (www.isrctn.com/; 18 April 2018)

Searching other resources

We contacted organizations, including the WHO and the Centers for Disease Control and Prevention (CDC), for ongoing and unpublished trials. The reference lists of all trials identified by the above methods were also consulted.

Data collection and analysis

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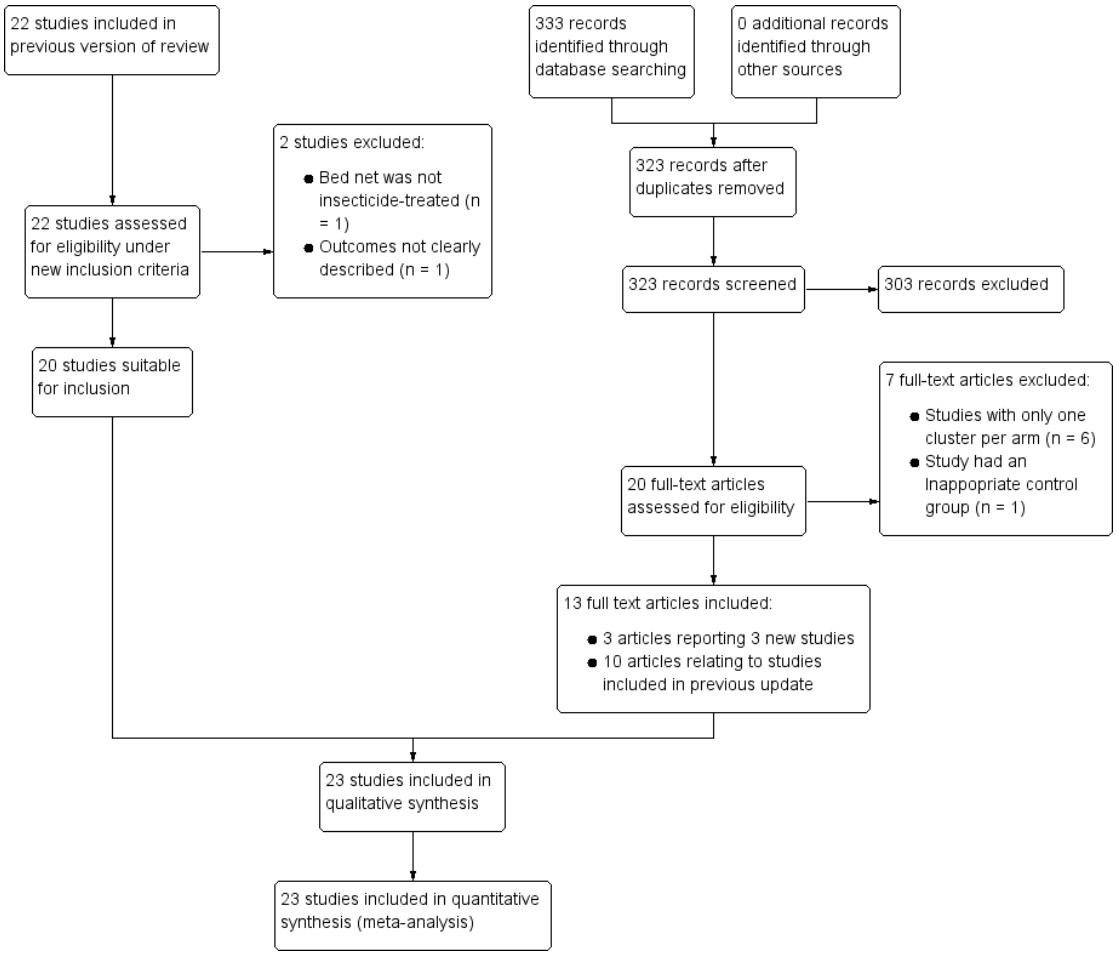
Selection of studies

One review author (JP) screened the titles and abstracts of articles identified by the literature searches for potential inclusion in the review. The full-text articles of potentially relevant trials were assessed using an eligibility form based on the inclusion criteria. Multiple publications of the same trial were included only once. Excluded studies are listed together with their reasons for exclusion in the Characteristics of excluded studies table. We have illustrated the study selection process in a PRISMA diagram (see Figure 1).

Figure 1. Study flow diagram.



Data extraction and management

One review author (JP) extracted information from each of the included studies (identified in both search processes) using pre-piloted electronic data extraction forms. In the case of missing data in studies from the initial search, we contacted the original study

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authors or the author of the original review (CL) for confirmation. In case of missing data in newly identified studies, we contacted the original study authors for clarification.

We extracted data on the following.

- Trial design: type of trial; length of follow-up; method of participant selection; sample size; and method of blinding of participants and personnel. For cRCTs we also recorded the number of clusters randomized, the number of clusters analysed, and method of adjustment for clustering.
- Participants: number of participants; inclusion/exclusion criteria.
- Intervention: description of intervention (active ingredient, dose, retreatment times, type of net); description of control.
- Outcomes: definition of outcomes; diagnostic method or surveillance method; passive or active case detection.
- Other: study location; malaria endemicity, entomological inoculation rate (EIR), primary vector species; *Plasmodium* species.

For dichotomous outcomes, we extracted the number of participants who experienced each outcome and the total number of participants in each treatment group. Where trials conducted multiple cross-sectional surveys during the intervention period, we took an average of the numerators and denominators across the total number of surveys. We selected this procedure in order to avoid inflating the denominator artificially by adding up the participants from repeated surveys. For count data outcomes, we extracted the number of outcomes in the treatment and control groups and the total person-time at risk in each group, or the rate ratio and a measure of variance (for example, standard error). For continuous outcomes, we extracted the mean and a measure of variance (standard deviation).

We considered the impact of ITNs on the primary outcome of child mortality from all causes likely to be age-dependent. In addition to extracting the total number of deaths in the total study population, where possible we extracted the number of deaths and total number of children within a high-risk age group of 1 to 59 months. This allowed an estimate for each age group of the number of deaths that can be avoided through the provision of ITNs.

Assessment of risk of bias in included studies

We assessed the risk of bias for each study using the Cochrane 'Risk of bias' tool (Higgins 2011). For each included cRCT, we also assessed the five additional criteria relating specifically to cRCTs listed in Section 16.3.2 of the *Cochrane Handbook for Systematic Reviews of Interventions*. We classified judgements of risk of bias as either low, high, or unclear risk of bias. We have summarized the results of the assessment in a 'Risk of bias' summary figure.

Measures of treatment effect

We compared intervention and control data using rate ratios, risk ratios (RRs), and mean differences, and presented all results with their associated 95% confidence intervals (CIs).

Unit of analysis issues

If included cRCTs had not adjusted for clustering in the analysis, we adjusted the data before combining it. We adjusted data by multiplying the standard errors by the square root of the design effect (Higgins 2011), which is determined by the intracluster correlation coefficient (ICC). If the trial did not report the ICC value, we used the ICC from a similar trial that reported the same outcome (Smithuis 2013).

Dealing with missing data

In case of missing data, we applied available-case analysis, only including data on the known results. The denominator was the total number of participants who had data recorded for the specific outcome. For outcomes with no missing data, we performed analyses on an intention-to-treat basis. We included all participants randomized to each group in the analyses and analysed participants in the group to which they were randomized.

Assessment of heterogeneity

We inspected forest plots for overlapping CIs and assessed statistical heterogeneity in each meta-analysis using the I^2 statistic and Chi^2 test values. We considered I^2 statistic values between 30% and 60% indicative of moderate heterogeneity; between 50% and 90% substantial heterogeneity; and between 75% and 100% considerable heterogeneity. We considered a Chi^2 test statistic with a P value greater than 0.10 indicative of statistically significant heterogeneity. We explored clinical and methodological heterogeneity through consideration of the trial populations, methods, and interventions, and by visualization of trial results.

Assessment of reporting biases

We intended to investigate reporting biases (such as publication bias) by assessing funnel plot asymmetry (Harbord 2006). However, as each meta-analysis included fewer than 10 trials, such an assessment was not possible.

Data synthesis

We analysed data using Review Manager 5 (RevMan 2014). As we detected no heterogeneity between the study types, we pooled data from both individual RCTs and cluster-adjusted cRCTs in a meta-analysis (Richardson 2016).

Based on the consideration of clinical, epidemiological, and methodological heterogeneity between the trials, we used a random-effects model.

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Certainty of the evidence

We assessed the certainty of the evidence using the GRADE approach (Guyatt 2011), rating each outcome as follows.

- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect.
- Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

As all the included studies were RCTs, the evidence for each outcome started as high certainty, but could be downgraded if there were valid reasons to do so within the following five categories: risk of bias, imprecision, inconsistency, indirectness, and publication bias (Balshem 2011). We summarized the certainty of the evidence for each outcome in a 'Summary of findings' table.
We drew on a review of entomological outcomes in the presence of insecticide resistance to inform our indirectness judgement in GRADE (Strode 2014).

Subgroup analysis and investigation of heterogeneity

We planned that if we detected substantial heterogeneity, we would perform a subgroup analysis of malaria transmission stability (stable malaria defined as an EIR of 1.0 and above, or unstable malaria defined as an EIR of less than 1.0). We additionally intended to subgroup cRCTs and individual RCTs. However, we detected substantial heterogeneity in only one meta-analysis, and as all of the included studies were cRCTs conducted in unstable malaria areas, the subgroup analyses would not have provided any insight into the heterogeneity.

Sensitivity analysis

We intended to perform a sensitivity analysis on the primary outcome to determine the effect of exclusion of trials judged to have a serious risk of bias, but we identified no such studies.

RESULTS

Description of studies

Results of the search

Our search of the databases identified a total of 333 new records. We considered 20 articles for full-text screening following title and abstract screening. From these, we identified three articles, reporting three new trials, that met our inclusion criteria, and five new articles relating to trials included in the previous update. The search also returned five articles that were included and referenced in the previous review. The remaining seven trials were excluded. We also screened the full texts of the 22 trials included in the previous version of the review against the inclusion criteria of the review update. Of these, we identified 20 trials for inclusion in the updated review. One record described four individual trials, conducted in separate regions of Latin America (Kroeger 1995 (Colombia); Kroeger 1995 (Ecuador); Kroeger 1995 (Peru Amazon); Kroeger 1995 (Peru Coast)). The study selection process is shown in Figure 1.

Included studies

Trial design and location

Of the 23 RCTs meeting the inclusion criteria, two were individually randomized. The remaining 21 trials were cRCTs. In 15 trials, the unit of randomization was the village or larger administration unit, while six trials used households as the unit of randomization. The two individual RCTs were analysed on an intention-to-treat basis.
Twelve trials were conducted in sub-Saharan Africa (Burkina Faso, Cameroon, Gambia (2), Ghana, Ivory Coast, Kenya (3), Madagascar, Sierra Leone, and Tanzania). Six trials were conducted in Latin America (Colombia, Ecuador, Nicaragua, Peru (2), and Venezuela). Four trials were conducted in the Greater Mekong subregion (Cambodia, Myanmar, and Thailand (2)), and one trial was conducted in Pakistan.
The three trials new to this update were cRCTs conducted in Cambodia, Myanmar, and Venezuela.

Participants

Eleven trials included the whole population of selected areas (typically in low-endemicity areas), while 12 trials restricted participation to specific age groups (typically children in high-endemicity areas). Two studies were conducted specifically in displaced-persons camps (Luxemburger 1994; Rowland 1996), and one study was restricted solely to migrant workers in the area (Kamol-Ratanakul 1992).

Intervention

The trials examined the impact of insecticide-treated bed nets (n = 19), treated hammock nets (n = 2), or treated curtains (n = 2). Additionally, one trial compared treated nets, treated curtains, and no bed nets or curtains (Sexton 1990).

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In some trials the intervention consisted of treating existing nets with an insecticide ('treatment of nets'), while in other trials the investigators provided treated mosquito nets or curtains to the population ('treated nets' and 'treated curtains').

Most nets or curtains were treated with permethrin (200 mg/m^2 (n = 3), 500 mg/m^2 (n = 9), or 1000 mg/m^2 (n = 1)). The remaining nets or curtains were treated with lambda-cyhalothrin (10 to 30 mg/m^2; n = 5) or deltamethrin (25 mg/m^2; n = 4), while one study used lambda-cyhalothrin (10 mg/m^2) for the first year and permethrin (500 mg/m^2) for the second year (Kroeger 1995 (Peru Coast)).

Approximately half of the trials used untreated nets as a control (n = 11), while the remaining trials used no net or curtain as a control (n = 12). The usage rate of the untreated nets was high (> 80%), except in one region in Peru, in which it was 63% (Kroeger 1995 (Peru Coast)), and in the Gambia (D'Alessandro 1995), in which it varied between 50% and 90% according to the area. No usage rate was provided for Rabarison 1995, Magris 2007, or Smithuis 2013.

Outcomes

Seven trials reported on our primary outcome of child mortality from all causes. Of these, six were conducted in highly malaria endemic areas in sub-Saharan Africa, and one was in conducted in Myanmar (Smithuis 2013). Two studies reported on the incidence of severe malaria episodes. Other outcomes reported throughout the studies included the prevalence, incidence, and cumulative incidence of each of *P falciparum*, *P vivax*, and any *Plasmodium* species.

Excluded studies

Of the 20 full texts we screened from the literature search update, we excluded seven articles. Six corresponded to four trials that were not truly RCTs as they included only one cluster per arm. The seventh article reported a trial that had an inappropriate control group, as most participants in both groups were regularly using ITNs.

We also excluded two trials that were included in the previous version of the review after screening against this update's modified inclusion criteria. The intervention in one trial was bed nets that were not treated with insecticide (Snow 1988), and the second trial did not describe the measured outcomes clearly (Zaim 1998). Further details are in the Characteristics of excluded studies table. Characteristics of the studies excluded after the previous literature search are described in Lengeler 2004.

Risk of bias in included studies

A detailed description of the 'Risk of bias' assessments against the following criteria are provided in each included trial's 'Risk of bias' table in the 'Characteristics of included studies' section. A summary is provided in the 'Risk of bias' summary figure (Figure 2).

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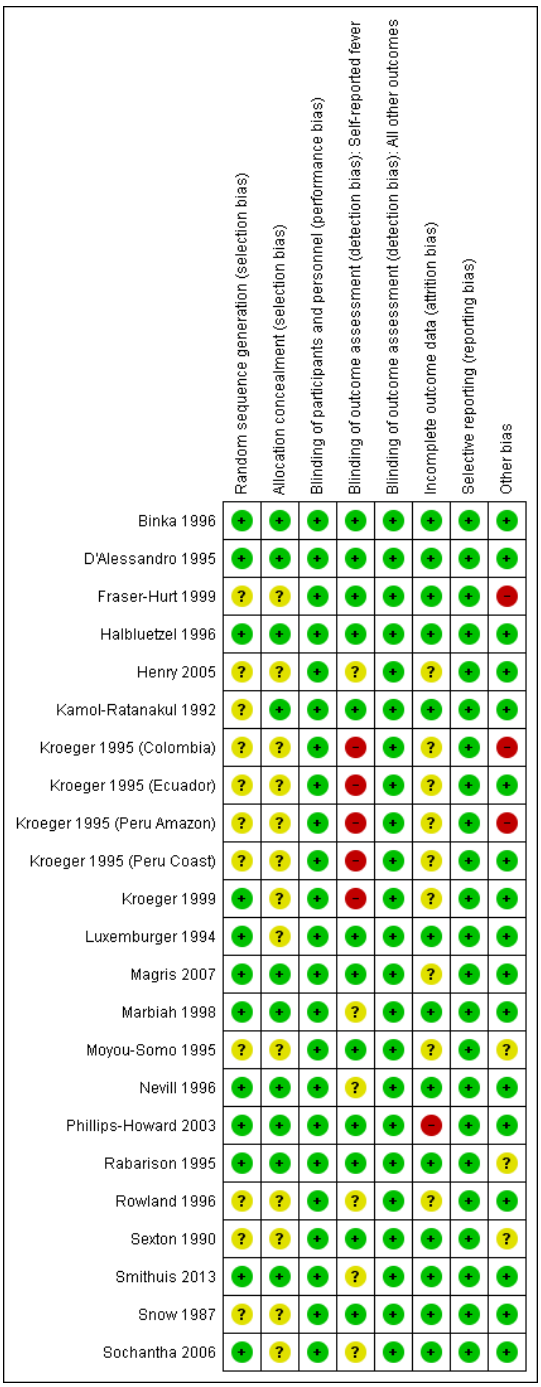
Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



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Allocation

Though each study described the distribution of clusters to intervention or control arms as random, in several instances the specific randomization and allocation concealment processes are not described. We considered such trials to have an unclear risk of bias. Randomization procedures, where described, typically involved a public lottery, or a computer-generated randomization sequence.

Blinding

Due to the nature of the intervention, it is difficult to blind participants and study personnel to the allocated intervention group, and blinding was only conducted in five trials (Kamol-Ratanakul 1992; Luxemburger 1994; Magris 2007; Rabarison 1995; Snow 1987). However, the outcomes evaluated here, that is infection, mortality, and morbidity from malaria, were considered unlikely to be affected by participant knowledge of intervention status. We therefore assumed each of the trials to be at low risk of performance bias.

The measurement of outcomes was also considered to be unaffected by intervention knowledge for mortality, severe malaria, and prevalence of malaria as collected from cross-sectional surveys. However, we considered that outcomes through participants' self reporting of fever may be influenced by knowledge of the allocated intervention group. If self reported cases were confirmed by microscopy or a rapid diagnostic test, we considered the risk of detection bias to be unclear. In five trials, cases were recorded solely on the basis of self reporting, without further confirmation (Kroeger 1995 (Colombia); Kroeger 1995 (Ecuador); Kroeger 1995 (Peru Amazon); Kroeger 1995 (Peru Coast); Kroeger 1999). We considered these trials to have a high risk of detection bias.

Incomplete outcome data

We considered one trial to be at high risk of attrition bias, as the study participants included children aged 1 to 59 months, but in cross-sectional surveys, only children aged 1 to 3 years were sampled (Phillips-Howard 2003). We judged the risk of bias to be unclear for nine trials that insufficiently reported the total numbers randomized and reasons for attrition.

Selective reporting

All included trials had a low risk of reporting bias.

Other potential sources of bias

We considered three trials to have a high risk of bias due to significant imbalances between intervention and control groups at baseline for one or more reported outcomes (Fraser-Hurt 1999; Kroeger 1995 (Colombia); Kroeger 1995 (Peru Amazon)). We judged trials that did not adequately report on baseline differences as at unclear risk of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Insecticide-treated bed nets and curtains compared to no nets for preventing malaria; **Summary of findings 2** Insecticide-treated bed nets and curtains compared to untreated nets for preventing malaria

Comparison 1: Insecticide-treated nets versus no nets

Twelve trials assessed this comparison: nine in sub-Saharan Africa, one in Cambodia, one in Myanmar and one in Pakistan

Child mortality from all causes

Five cRCTs reported child mortality from all causes. Four were conducted in highly malaria endemic areas in sub-Saharan Africa, and one newly identified trial was conducted in Myanmar (Smithuis 2013). The latter trial was small and contributed to 0.1% of the overall weight of the analysis. Pooled analysis of five trials showed that mortality from all causes was 17% lower in children using an ITN than those without a net (rate ratio 0.83, 95% CI 0.77 to 0.89: 5 trials, 200,833 participants Analysis 1.1). This corresponds to a saving of 5.6 lives (95% CI 3.6 to 7.6) each year for every 1000 children protected with ITNs. We assessed the mortality from all causes rate in a high-risk age group (1 to 59 months) using data from four trials (Binka 1996; Halbluetzel 1996; Nevill 1996; Phillips-Howard 2003), finding a saving of 6.4 lives (95% CI 4.16 to 8.69) for every 1000 children protected with ITNs.

Uncomplicated clinical episodes

Five cRCTs reported the impact of ITNs on the incidence of uncomplicated *P falciparum* episodes. Four trials were conducted in highly malaria endemic areas in sub-Saharan Africa, and one newly identified trial was conducted in Cambodia (Sochantha 2006). One trial, conducted in an area of known insecticide resistance in Ivory Coast, demonstrated a rate ratio of 0.43 (95% CI 0.25 to 0.74). Overall, the reduction in the rate of clinical episodes was almost 50% (rate ratio 0.55, 95% CI 0.48 to 0.64; 5 trials, 35,551 participants Analysis 1.2). Additionally, two trials reported the impact of ITNs on the proportion of people experiencing a clinical episode of *P falciparum* within a given time frame (cumulative incidence). A similar overall reduction was seen to that of the incidence rate (RR 0.44, 95% CI 0.31 to 0.62; 2 trials, 10,967 participants, Analysis 1.3).

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Two cRCTs, conducted in Myanmar and Pakistan respectively, reported the impact of ITNs on the cumulative incidence of uncomplicated *P vivax* episodes. Clinical episodes of *P vivax* were reduced by 39% in people using an ITN (RR 0.61, 95% CI 0.48 to 0.77; 2 trials, 10,967 participants Analysis 1.4). One trial also reported the cumulative incidence of uncomplicated episodes of any *Plasmodium* species, finding a 50% reduction in the ITN group (RR 0.50, CI 0.28 to 0.90; 1 trial, 8,395 participants, Analysis 1.5) (Smithuis 2013).

Prevalence

Six cRCTs reported the impact of ITNs on *P falciparum* prevalence. One newly identified study that was conducted in Myanmar contributed 6.8% of the overall weight of the analysis (Smithuis 2013). Prevalence was reduced by 17% with ITN use (RR 0.83, 95% CI 0.71 to 0.98; 6 trials, 18,809 participants, Analysis 1.6). Two studies, conducted in Myanmar and Pakistan respectively, reported the impact of ITNs on the prevalence of *P vivax*. We found no difference between ITN and no-nets groups (RR 1.00, 95% CI 0.75 to 1.34; 2 trials, 10,967 participants, Analysis 1.7).

Severe malaria episodes

Two trials evaluated severe malarial disease as an outcome, using passive and hospital/health centre-based case ascertainment. Due to the very low number of cases in Myanmar, the trial contributed only 0.3% of the overall weight of the analysis. Pooled analysis showed a 44% reduction in the incidence of severe malaria episodes in the ITN group (rate ratio 0.56, 95% CI 0.38 to 0.82; 2 trials, 31,173 participants, Analysis 1.8).

Anaemia

Five trials reported the mean haemoglobin in ITN and no-nets arms. Pooled analysis of the trials showed that ITNs were associated with a mean difference of a 1.29 increase in percentage PCV (95% CI 0.42 to 2.16; 5 trials, 11,489 participants, Analysis 1.9).

Comparison 2: Insecticide-treated nets versus untreated nets

Eleven trials assessed this comparison: three in sub-Saharan Africa, six in Latin America, and two in Thailand.

Child mortality from all causes

Two cRCTs, conducted in highly malaria endemic areas in sub-Saharan Africa, reported child mortality from all causes. Pooled analysis of the trials showed that mortality from all causes was 33% lower in children using an ITN than in those using an untreated net, but as the CI includes no effect, the result is not statistically significant (rate ratio 0.67, 95% CI 0.36 to 1.23; 2 trials, 25,389 participants, Analysis 2.1). This corresponds to a saving of 3.5 lives (95% CI -2.4 to 6.8) each year for every 1000 children protected with ITNs. The mortality from all causes rate in a high-risk age group (1 to 59 months) was determined using data from one trial (D'Alessandro 1995). In this group, the saving is 8.0 lives (95% CI -5.6 to 15.57) for every 1000 children protected with ITNs.

Uncomplicated clinical episodes

Four cRCTs and one individual RCT reported the impact of ITNs on the incidence of uncomplicated *P falciparum* episodes. The overall analysis showed that ITNs contributed to a 42% reduction in the rate of clinical episodes (rate ratio 0.58, 95% CI 0.44 to 0.78; 5 trials, 2,036 participants, Analysis 2.2).

Two cRCTs and one individual RCT, conducted in Thailand (two) and Venezuela, reported the incidence of uncomplicated *P vivax* episodes. The overall decrease in the rate of clinical episodes of *P vivax* in people using an ITN was not statistically significant (rate ratio 0.73, 95% CI 0.51 to 1.05; 3 trials, 1,535 participants, Analysis 2.3). The reduction seen in the cumulative incidence of uncomplicated episodes of *P vivax,* reported by three trials in Latin America, was also not statistically significant (RR 0.59, CI 0.30 to 1.18; 3 trials, 23,506 participants, Analysis 2.4). Two trials also reported the cumulative incidence of uncomplicated episodes of any *Plasmodium* species, reporting a reduction that was not statistically significant (RR 0.47, 95% CI 0.17 to 1.28, 2 trials, 8,082 participants, Analysis 2.5).

Prevalence

Two cRCTs in sub-Saharan Africa and one individual RCT in a displaced persons camp in Thailand (accounting for 3.3% of the overall weight of the analysis) reported the impact of ITNs versus untreated nets on prevalence of *P falciparum*. Pooled analysis showed that the reduction in prevalence was not significant (RR 0.91, 95% CI 0.78 to 1.05; 3 trials, 2,259 participants, Analysis 2.6).

The trial conducted in Thailand also reported a reduction in *P vivax* prevalence that was not statistically significant (RR 0.68, 95% CI 0.25 to 1.85; 1 trial, 350 participants, Analysis 2.7; Luxemburger 1994), and one trial reported a massive reduction in the prevalence of any *Plasmodium* species (RR 0.17, 0.05 to 0.53; 1 trial, 924 participants, Analysis 2.8; Magris 2007). However the results are of limited value as there was only a single trial in each analysis.

Severe malaria episodes

No trials evaluating this comparison reported the outcome of severe malaria episodes.

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Anaemia

Three cRCTs reported the mean haemoglobin in ITN and untreated-net study arms. For two studies, information on the mean PCV, total number sampled, and standard deviation were all available, permitting pooling of the data in a meta-analysis (D'Alessandro 1995; Snow 1987). Pooled analysis showed that ITNs were associated with a mean difference of a 0.48 increase in the percentage PCV that was not statistically significant (95% CI -0.54 to 1.50; 2 trials, 1,909 participants, Analysis 2.9).

The third trial also reported the mean haemoglobin in both arms over two surveys. This trial reported a variable impact of ITNs compared to untreated nets, with a mean PCV difference of -1.2 (624 participants) in the first survey and +1.5 (516 participants) in the second survey.

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ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Insecticide-treated bed nets and curtains (ITNs) compared to untreated nets (UTNs) for preventing malaria

Patient or population: people of all ages living in malaria transmission settings
Setting: Colombia 1993 (Kroeger 1995 (Colombia)); Ecuador 1992 (Kroeger 1995 (Ecuador)); Gambia 1993 (D'Alessandro 1995); Gambia 1985 (Snow 1987); Madagascar 1994 (Rabarison 1995); Nicaragua 1996 (Kroeger 1999); Peru Amazon 1992 (Kroeger 1995 (Peru Amazon)); Peru Coast 1993 (Kroeger 1995 (Peru Coast)); Thailand 1988 (Kamol-Ratanakul 1992); Thailand 1991 (Luxemburger 1994); Venezuela 2000 (Magris 2007)
Intervention: ITNs
Comparison: UTNs

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Risk with UTNs	Risk with ITNs				
Child mortality from all causes	Children of all ages		Rate ratio 0.67 (0.36 to 1.23)	25,389 (2 RCTs)	⊕⊕⊕◯ MODERATE[a,b] *due to imprecision*	Insecticide-treated bed nets and curtains probably reduce all-cause child mortality compared to UTNs
	10.6 per 1000	7.1 per 1000 (3.8 to 13.0)				
	Children aged 1 to 59 months					
	24.3 per 1000	16.3 per 1000 (8.8 to 29.9)				
Plasmodium falciparum uncomplicated episodes	289 per 1000	167 per 1000 (124 to 228)	Rate ratio 0.58 (0.44 to 0.78)	2,036 (5 RCTs)	⊕⊕⊕⊕ HIGH[a,c]	Insecticide-treated bed nets and curtains reduce the incidence of uncomplicated *P falciparum* malaria episodes compared to UTNs.
Plasmodium vivax uncomplicated episodes [l]	143 per 1000	104 per 1000 (73 to 150)	Rate ratio 0.73 (0.51 to 1.05)	1,535 (3 RCTs)	⊕⊕◯◯ LOW[a,b,d] *due to imprecision and indirectness*	Insecticide-treated bed nets and curtains may reduce the incidence of uncomplicated *P vivax*

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						malaria episodes compared to UTNs.
Any *Plasmodium* spp. uncomplicated episodes (cumulative incidence)	69 per 1000	32 per 1000 (12 to 88)	Risk ratio 0.47 (0.17 to 1.28)	8,082 (2 RCTs)	⊕⊕⊕◯ MODERATE[a,b,e] *due to imprecision*	Insecticide-treated bed nets and curtains probably reduce the incidence of uncomplicated malaria episodes of any species compared to UTNs
P falciparum prevalence	378 per 1000	344 per 1000 (295 to 397)	Risk ratio 0.91 (0.78 to 1.05)	2,259 (3 RCTs)	⊕⊕⊕◯ MODERATE[a,b] *due to imprecision*	Insecticide-treated bed nets and curtains probably reduce the prevalence of *P falciparum* malaria compared to UTNs.
P vivax prevalence	39 per 1000	27 per 1000 (10 to 73)	Risk ratio 0.68 (0.25 to 1.85)	350 (1 RCT)	⊕◯◯◯ VERY LOW[a,f,g] *due to imprecision and indirectness*	It is unclear if ITNs reduce the prevalence of *P vivax* malaria compared to UTNs.
Any *Plasmodium* spp. prevalence	104 per 1000	18 per 1000 (5 to 55)	Risk ratio 0.17 (0.05 to 0.53)	924 (1 RCT)	⊕◯◯◯ VERY LOW[a,h,i] *due to imprecision and indirectness*	It is unclear if ITNs reduce the prevalence of malaria, regardless of species, compared to UTNs
Anaemia (mean packed cell volume)	32.8	33.3 (32.3 to 34.3)	Mean difference 0.48 (-0.54 to 1.50)	1,909 (2 RCTs)	⊕⊕◯◯ LOW[a,j,k] *due to imprecision and indirectness*	Insecticide-treated bed nets and curtains may increase the mean packed cell volume compared to UTNs

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
Abbreviations: CI: confidence interval; **RCT:** randomized controlled trial; **ITN**: Insecticide-treated net; **UTN**: untreated net

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a] Not downgraded for indirectness: for most included studies, it is unclear whether insecticide resistance was present. The review authors judge that there is not convincing evidence that insecticide resistance would reduce the impact of ITNs on the included epidemiological outcomes. A previous review that included entomological outcomes showed the difference in mosquito mortality risk using ITNs compared with UTNs modestly decreased as insecticide resistance increased (Strode 2014). However, mosquito mortality risk remained significantly higher for ITNs than for UTNs, regardless of the resistance status.

[b] Downgraded one level for imprecision: the confidence interval includes both a sizable decrease and an increase in the absolute number of events.

[c] Not downgraded for inconsistency: despite significant heterogeneity (I^2 value of 75%), each trial consistently shows an effect in favour of ITNs.

[d] Downgraded one level for indirectness: the three studies had restrictive participant inclusion criteria. The largest weighted study included only children from a displaced persons camp in Thailand. The second study included only migrant workers also in Thailand. The third included only children younger than 10 years in Venezuela. It is not clear how confidently the information can be applied to other populations.

[e] Not downgraded for risk of bias: although the lack of participant blinding could potentially influence the likelihood of reporting a fever, we did not consider this likely to have seriously affected the results of the studies.

[f] Downgraded two levels for imprecision: the confidence interval includes both a sizable decrease and increase in the absolute number of events. Additionally, the small sample size and low number of events are insufficient for confidently estimating the effect size.

[g] Downgraded two levels for indirectness: the results come from only one study, conducted only in children living in displaced persons camps in Thailand. It is not clear how confidently the information can be applied to other populations.

[h] Downgraded one level for imprecision: the small sample size and low number of events are insufficient for confidently estimating the effect.

[i] Downgraded two levels for indirectness: the results come from only one study, conducted only in children living in the Amazon rainforest. It is not clear how confidently the information can be applied to other populations.

[j] Downgraded one level for indirectness: the results come from two studies that were both conducted in Gambia and only included children under the age of 10. It is not clear how confidently the information can be applied to other populations.

[k] Downgraded one level for imprecision: the confidence interval includes both a decrease and increase in the mean packed cell volume.

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[l]The cumulative incidence of *P vivax* clinical episodes was also reported (Analysis 2.4: RR 0.58, 95% CI 0.30 to 1.14, low-certainty evidence). As this is consistent with the effect on the incidence rate, we did not present both results in the 'Summary of findings' table.

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DISCUSSION

Summary of main results

We identified three new trials for inclusion that have been published since the previous version of this review (Lengeler 2004). The new trials did not affect the conclusions of our review. Each reported outcome showed a trend that favoured ITNs, both in comparison to no nets (see Summary of findings for the main comparison) and untreated nets (see Summary of findings 2). Insecticide-treated nets were shown to reduce child mortality from all causes by almost one-fifth compared to children sleeping without a net (high-certainty evidence). Uncomplicated clinical episodes of malaria were reduced by almost one-half (high-certainty evidence) and severe malaria episodes were also reduced by more than 40% (high-certainty evidence). The prevalence of*P falciparum* was reduced by 17% (high-certainty evidence), although a pooled analysis of two trials showed no impact on prevalence of *P vivax* (low-certainty evidence). We found similar results when ITNs were compared to untreated nets, with child mortality from all causes reduced by one-third (moderate-certainty evidence). Uncomplicated clinical episodes of *P falciparum* and *P vivax* were reduced by 42% (high-certainty evidence) and 27% (low-certainty evidence), respectively. Reductions in the prevalence of *P falciparum* and *P vivax* were not significant (moderate- and very low certainty evidence).

Overall completeness and applicability of evidence

Although published more recently than the studies included in the previous review, two of the newly included studies were conducted in the year 2000 (Magris 2007; Smithuis 2013), and the third was conducted in 2001 (Sochantha 2006). Each of the new studies was therefore conducted no later than the date of publication of the previous review, and consequently the additional insight they can provide into the effectiveness of ITNs today, in the presence of widespread insecticide resistance, is limited. For most of the included studies, it was unclear whether insecticide resistance was present. However, one included study was specifically conducted in an area of known high insecticide resistance (Henry 2005). Although the study was carried out between July 1999 and June 2000, local populations of *Anopheles gambiae s.s.* were strongly resistant to pyrethroids, with a knockdown resistance (*kdr*) allelic frequency of around 90%. *Anopheles funestus*, another local primary vector, was still susceptible to these insecticides. The impact on *P falciparum* uncomplicated episodes was the only reported outcome eligible for inclusion in this review, showing a reduction in the rate of clinical episodes in the ITN group of 57%. This was in fact the greatest impact reported by any study for this outcome. Hence the study provides no evidence that ITNs became less effective in the presence of high *kdr* frequency.

Certainty of the evidence

We found no convincing evidence, either in this review or in the currently available literature, that insecticide resistance would significantly affect the impact of ITNs on the epidemiological outcomes reported here. A previous review that included entomological outcomes showed that the difference between mosquito mortality risk using ITNs compared with use of untreated nets decreased modestly as insecticide resistance increased (Strode 2014). However, mosquito mortality risk remained significantly higher for ITNs than for untreated nets, regardless of the resistance status. Additionally, despite reports of moderate-to-high pyrethroid resistance across many endemic countries, the distribution of ITNs continues to impact on malaria incidence and prevalence (Alout 2017). Until there is evidence that insecticide resistance is reducing the impact of ITNs on epidemiological outcomes, we adjudge that we should not decrease our certainty in the estimate of the effect of ITNs based on the presence of insecticide resistance. A full assessment of the certainty of the evidence for each outcome is presented in the 'Summary of findings' tables.

Potential biases in the review process

If included cRCTs did not adjust for clustering in the analysis, we adjusted the data before it was combined. A potential bias arises for trials that did not report the ICC value, for which we used the ICC from a similar trial that reported the same outcome (Smithuis 2013). This approximated ICC value may lead to somewhat inaccurate sizes of CIs for such trials, although the estimate of the effect would not be affected.

Agreements and disagreements with other studies or reviews

Despite being published before most trials included in this review were conducted, Choi 1995's meta-analysis reported a similar impact of ITNs on the incidence of malaria infection. In comparison to participants receiving no nets, the incidence was reduced by 51%. In the subset of trials comparing ITNs to UTNs, a smaller, but still significant, reduction of 24% was seen. More recently, Yang 2018 conducted a meta-regression of 39 studies published since the year 2000. The review differentiated classic ITNs, which require re-treating at least once per year, from long-lasting insecticide-treated nets (LLINs), which use newer fabric technologies to remain effective for several years. The meta-regression found that ITNs and LLINs respectively reduce the incidence of malaria by 41% and 56% when compared to no nets. Though no other outcomes were assessed in either study, the finding supports the

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suggestion that treated nets have remained effective at preventing malaria cases in recent decades, despite growing concerns about insecticide resistance in malaria vectors. Unlike this review, both Choi 1995 and Yang 2018 included field trials of any study design, as long as they had a concurrent control group. Importantly, the reviews did not consider that cRCTs cannot be analysed with the same methods used when interventions are allocated on an individual level. The confidence limits presented in these reviews may therefore be deceptive. The more conservative confidence intervals presented in this review, calculated in line with the design effect of the studies, provide a more dependable indication of the lowest and largest possible effect sizes.

AUTHORS' CONCLUSIONS

Implications for practice

Despite the increase in insecticide resistance frequency and intensity in populations of malaria vectors across the world, the evidence for the effectiveness of ITNs for reducing malaria-related illness and death remains strong.

Implications for research

Although we judge that there is currently no strong evidence that insecticide resistance is reducing the impact of ITNs on epidemiological outcomes, future research should continue to concentrate on monitoring the spread of insecticide resistance and understanding if there is a relationship between observed resistance and reduced effectiveness of insecticide-based vector control interventions.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Binka 1996

Methods	Study design: cluster RCT (cRCT) Unit of allocation: clusters of compounds (average 120 compounds and 1400 people/cluster) Number of units: 48:48 Length of follow-up: 2 years (July 1993 to June 1995). Outcome assessment: mortality was monitored by village reporters in addition to demographic data collected every 3 months by rolling census. Adjustment: confidence limits for the rate ratio were calculated taking into account the cluster randomization
Participants	Number of participants: approximately 134,400 Inclusion criteria: children < 10 years
Interventions	Intervention: bed net Insecticide and dosage: permethrin suspension (0.5 g/mL) Retreatment: every 6 months Usage: year 1: 97% July-Dec, 65% Jan-June; year 2: 72% July-Dec, 50% Jan-June Control: no net
Outcomes	Outcomes measured: mortality rate
Notes	Study location: Kassena-Nankana district, Ghana EIR: 100 to 1000 Malaria transmission: variable but high Main vectors: *Anopheles gambiae s.s.*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Open lotteries were conducted during 21 community meetings to randomly select the clusters that were to receive the impregnated bed nets
Allocation concealment (selection bias)	Low risk	Open lottery conducted.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not possible to blind participants and personnel, but this was not likely to introduce bias to the outcome of mortality
Blinding of outcome assessment (detection bias) Self-reported fever	Low risk	This outcome was not assessed.

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Binka 1996 (*Continued*)

Blinding of outcome assessment (detection bias) All other outcomes	Low risk	Not possible to blind outcome assessors, but this was not likely to introduce bias when measuring the outcome of mortality
Incomplete outcome data (attrition bias) All outcomes	Low risk	High estimated sensitivity to all deaths in the study area
Selective reporting (reporting bias)	Low risk	All expected outcomes reported.
Other bias	Low risk	Recruitment bias: low risk Baseline imbalance: the pre-intervention mortality rates were comparable (23.0 and 23.5/1000 child years in the treated and control clusters respectively) Loss of clusters: none Incorrect analysis: adjusted Comparability with RCTs randomizing individuals: suitable due to cluster-adjusted confidence intervals (CIs)

D'Alessandro 1995

Methods	Study design: cRCT Unit of allocation: village (52 pairs of villages formed on the basis of size, after stratification by 5 geographical areas) Number of units: 58:52 Length of follow-up: 12 months Dropout rate unknown, but immigration/emigration rates were low (< 5% per year) Mortality monitored by village reporters and yearly census. Morbidity surveys were conducted once, at the peak of the transmission season in October (n = 1520 in 50 villages). All surveys were community-based
Participants	Inclusion criteria: children aged 0 to 9 years and living in the area were eligible at the start, but the analysis was later restricted to children aged 1 to 59 months (n = 25,000) Exclusion criteria: no explicit exclusion criteria except absence of written consent
Interventions	Intervention: treatment of existing bed nets in the frame of a national programme; target dose 200 mg/m^2 permethrin; impregnation done by village health workers with the assistance of other community members and under the supervision of community health nurses; retreatment was not done during the 1-year follow-up period since the transmission season lasts only about 4 months Control: untreated bed nets Usage rate around 70% in both intervention and control areas (varied between 50% and 90% according to the area)
Outcomes	• Overall mortality (1 to 59 months) • Prevalence of parasitaemia (any) • Prevalence of high parasitaemia (> 5000 trophozoites/μL)

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	• Anaemia (mean packed cell volume) • Prevalence of splenomegaly (1 to 5 Hackett) • Impact on nutritional status (weight-for-age, weight-for-height)
Notes	Study location: 5 distinct areas spread over the whole of the Gambia (all rural areas) EIR: 1 to 10 Malaria endemicity: hyperendemic Baseline parasite rate in children 12 to 59 months: 39% Main vector: *Anopheles gambiae s.l.* *P vivax* malaria: very low; not taken into account for analysis Access to health care moderately easy.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Intervention allocation by public lottery (information provided by CL)
Allocation concealment (selection bias)	Low risk	Low risk given the above intervention allocation procedure
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding described, but the review authors judge that the outcomes of mortality and malaria infection were unlikely to be influenced by the lack of blinding to participants and personnel
Blinding of outcome assessment (detection bias) Self-reported fever	Low risk	This outcome was not assessed.
Blinding of outcome assessment (detection bias) All other outcomes	Low risk	No blinding of outcome assessors described, but this was unlikely to influence the outcome measurement for mortality or parasite prevalence
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All expected outcomes reported.
Other bias	Low risk	Recruitment bias: low risk Baseline imbalance: the pre-intervention mortality rates were adjusted for in the analysis Loss of clusters: none Incorrect analysis: adjusted

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D'Alessandro 1995 (*Continued*)

		Comparability with RCTs randomizing individuals: unclear

Fraser-Hurt 1999

Methods	Study design: individual RCT Unit of allocation: individual Number of units: 122 Length of follow-up: 6 months Outcome assessment: monthly cross-sectional surveys were conducted. Thick blood films were prepared at enrolment and at each survey
Participants	Number of participants: 122 Inclusion criteria: children aged 5 to 24 months who were afebrile, not using a bed net, and not taking chloroquine
Interventions	Type of intervention: bed net (n = 61) Insecticide and dosage: permethrin (500 mg/m^2) Retreatment: after 3 months and at the end of the trial Usage: 97% Control: no net (n = 61)
Outcomes	Outcomes measured: *P falciparum* prevalence
Notes	Study location: Kiberege, Kilombero District, southern Tanzania EIR: approximately 300 Malaria transmission: intense and perennial Main vectors: *Anopheles gambiae s.l.* and *Anopheles funestus*

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Individuals allocated randomly, but the randomization process is not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel were not blinded to intervention group, but the review authors judge that this was unlikely to impact on the outcome of prevalence
Blinding of outcome assessment (detection bias) Self-reported fever	Low risk	This outcome is not assessed.

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Fraser-Hurt 1999 (*Continued*)

Blinding of outcome assessment (detection bias) All other outcomes	Low risk	Outcome assessors not blinded, but all participants were surveyed using objective blood smear examination, so this was unlikely to introduce bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data very minimal and balanced in numbers across the intervention groups (1 from each)
Selective reporting (reporting bias)	Low risk	All expected outcomes reported.
Other bias	High risk	Recruitment bias: low risk Baseline imbalance: the pre-intervention prevalence was substantially different between the intervention group (54.1%) and control group (65%)

Halbluetzel 1996

Methods	Study design: cRCT Unit of allocation: groups of villages (8 pairs of "clusters" (on average 10 villages) formed on the basis of baseline mortality and geographic similarity) Number of units: 8:8 Length of follow-up: 24 months Mortality was monitored by village reporters and yearly census. A cross-sectional morbidity survey was conducted once, at the peak of the transmission season in September 1995 (n = 800 in 84 villages). All surveys were community-based
Participants	Number of participants: 16,540 Inclusion criteria: children aged 0 to 59 months living in the area (newborns were excluded from the analysis) Exclusion criteria: no explicit exclusion criteria except absence of written consent
Interventions	Intervention: permethrin-treated curtains on windows, door, and eaves; target dose of 1000 mg/m^2; every house used for sleeping in the intervention clusters fitted with the curtains and retreated every 6 months Control: no curtains
Outcomes	• Overall mortality (1 to 59 months) • Prevalence of parasitaemia (any) • Prevalence of high parasitaemia (> 5000 trophozoites/μL) • Anaemia (mean haemoglobin in g/dL)
Notes	Study location: Oubritenga Province, 30 km north of Ouagadougou, Burkina Faso, in a rural area EIR: 300 to 500 Malaria endemicity: holoendemic Baseline parasite rate in children aged 6 to 59 months: 85%

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	Main vectors: *Anopheles gambiae s.l.* and *Anopheles funestus* *P vivax* malaria: 0% Dropout rate unknown, but immigration/emigration rates were low (2% per year) Access to health care considered poor.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Intervention allocation by public lottery (information provided by CL)
Allocation concealment (selection bias)	Low risk	Low risk given the above intervention allocation procedure
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not possible to blind participants and personnel, but the review authors do not consider this likely to introduce bias for the outcome of mortality
Blinding of outcome assessment (detection bias) Self-reported fever	Low risk	This outcome was not assessed.
Blinding of outcome assessment (detection bias) All other outcomes	Low risk	No blinding, but the review authors judge that the outcome and the outcome measurement were not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	High estimated sensitivity to all deaths in the study area
Selective reporting (reporting bias)	Low risk	All expected outcomes reported.
Other bias	Low risk	Recruitment bias: low risk Baseline imbalance: the pre-intervention mortality rates were adjusted for Loss of clusters: none Incorrect analysis: adjusted Comparability with RCTs randomizing individuals: suitable with adjusted CIs

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Henry 2005

Methods	Study design: cRCT Unit of allocation: village (allocation of 8 villages by paired randomization) Number of units: 4:4 Length of follow-up: 12 months Outcome assessment: active case surveillance by repeated cross-sectional surveys. Blood smear taken from every sick child, as assessed by nurse visit. Generalized estimating equation (GEE) applied for clustered data
Participants	Number of participants: 426 Inclusion criteria: children aged 0 to 59 months
Interventions	Intervention: bed net (n = 210) Insecticide and dosage: lambda-cyhalothrin formulated as a capsule suspension (15 mg a.i./m^2) Retreatment: nets dipped again after 6 months. Usage: average coverage rate with ITNs ranged from 76.7% to 84.0% in different villages. Control: no net (n = 216)
Outcomes	Outcomes measured: cumulative incidence of uncomplicated episodes
Notes	Study location: Korhogo, in the North of Côte d'Ivoire. High knockdown resistance (*kdr*) resistance EIR: 55 Malaria transmission: baseline prevalence of 82% in 1997 before implementation Main vectors: *Anopheles gambiae s.s.* and *Anopheles funestus. A gambiae* was strongly resistant to pyrethroids with a *kdr* allelic frequency of around 90%. *A funestus* was still susceptible to these insecticides.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	It is stated that the village chosen from each matched pair to receive ITN was randomly selected, but no details provided
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not possible to blind participants and personnel, but this was not likely to introduce bias to the outcome of malaria infection
Blinding of outcome assessment (detection bias) Self-reported fever	Unclear risk	Nurse examining and recording cases of sickness at the home would have been aware of study group being visited. Unclear if technicians examining blood slides were blinded to the study group

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Henry 2005 (*Continued*)

Blinding of outcome assessment (detection bias) All other outcomes	Low risk	These outcomes were not assessed.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Missing outcome data were balanced across the intervention groups. Reasons for missing data given, but only as a total and not for each intervention group, possibly masking biases (58 total deaths). An imbalance between the groups may have introduced bias to the examined outcomes
Selective reporting (reporting bias)	Low risk	All stated outcomes reported.
Other bias	Low risk	Recruitment bias: low risk Baseline imbalance: baseline figures comparable for prevalence (P = 0.35) and incidence (P = 0.36) Loss of clusters: none Incorrect analysis: adjusted Comparability with RCTs randomizing individuals: suitable for comparison

Kamol-Ratanakul 1992

Methods	Study design: cRCT Unit of allocation: household (average 4.8 per household) stratified by malaria endemicity Number of units: 26:28 Length of follow-up: 8 months (November 1987 to July 1988) Outcome assessment: morbidity rates monitored longitudinally by weekly follow-up, at which blood slides were taken systematically
Participants	Number of participants: 261 Inclusion criteria: migrant workers who had migrated to the study area more than 6 months prior to interview
Interventions	Intervention: bed net (n = 126) Insecticide and dosage: permethrin; 500 mg/m^2 Retreatment: not stated Usage: compliance 70% to 80% Control: untreated net (n = 135) compliance 70% to 80%
Outcomes	Outcomes measured: incidence of clinical episodes for both *P falciparum* and *P vivax*
Notes	Study location: Bothong District, Chonburi, Thailand EIR: low Malaria transmission: unstable Main vectors:

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	Anopheles dirus % *P vivax* cases: 43%; analysed separately

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomization scheme stated but not described.
Allocation concealment (selection bias)	Low risk	1 investigator who was not otherwise involved in the care or evaluation of participants prepared the randomization
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were blinded to treated or untreated net.
Blinding of outcome assessment (detection bias) Self-reported fever	Low risk	Participants and outcome assessors were blinded to treated or untreated net
Blinding of outcome assessment (detection bias) All other outcomes	Low risk	Outcome assessors were blinded to treated or untreated net.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomized participants included in follow-up.
Selective reporting (reporting bias)	Low risk	All expected outcomes reported.
Other bias	Low risk	Recruitment bias: low risk Baseline imbalance: the pre-intervention history of malaria in each group did not differ significantly

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Kroeger 1995 (Colombia)

Methods	Study design: cRCT Unit of allocation: village (22 villages were paired according to size, geographic location, net coverage, and malaria incidence at baseline; 1 village within each pair was then randomized to receive the intervention) Number of units: 11:11 Length of follow-up: 12 months (February 1993 to February 1994) Outcome assessment: cross-sectional survey carried out during the peak of the malaria season at baseline and 1 year post-intervention. Adjustment: none
Participants	Number of participants: 5632 Inclusion criteria: all inhabitants of the study area. % children under 15 = 50.6%
Interventions	Intervention: community programme for sales and promotion of bed nets, and free net treatment (n = 2295) Insecticide and dosage: lambda-cyhalothrin treatment of existing bed nets; target dose 10 to 30 mg/m^2 Retreatment: not stated Usage: nearly 60% of all existing nets were treated at least once Control: untreated net (n = 2337). Usage was very high (96% coverage)
Outcomes	Outcomes measured: period-prevalence (last 2 weeks or last 4 months) of reported "malaria episodes" assessed during the peak of the malaria season (February to March) Although no systematic parasitological confirmation was done, quality control procedures ensured adequate accuracy. (According to a pilot phase, about 88% to 96% of the self diagnoses were based on the same criteria as health professionals. In addition, time trends were compared to those obtained from routine data.)
Notes	Study location: lower Rio San Juan, Departamente Choco on the Pacific Coast, Colombia EIR: < 1 Malaria transmission: hypoendemic and unstable with marked seasonal variation Main vectors: *Anopheles nevai* % *P vivax* cases: < 41.5%

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	It was stated that villages were paired and randomly allocated, but randomization programme is not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not possible to blind participants and personnel, but the review authors judge that this lack of blinding was unlikely to have affected the outcome of malaria infection

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Kroeger 1995 (Colombia) (*Continued*)

Blinding of outcome assessment (detection bias) Self-reported fever	High risk	As participants were not blinded, this may introduce bias for the outcome measurement, particularly as the reporting of cases is subject to participants self reporting and recalling over a 4-month period
Blinding of outcome assessment (detection bias) All other outcomes	Low risk	These outcomes were not assessed.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting of attrition to permit judgement
Selective reporting (reporting bias)	Low risk	Outcomes reported are those expected, as they are in line with a series of trials conducted by the same authors across South America
Other bias	High risk	Recruitment bias: low risk Baseline imbalance: 4-month incidence rate significantly lower in intervention group Loss of clusters: none Incorrect analysis: no adjustment to CIs to account for clustering Comparability with RCTs randomizing individuals: not comparable unless clustering is adjusted for by review authors

Kroeger 1995 (Ecuador)

Methods	Study design: cRCT Unit of allocation: village (14 villages were paired according to size, geographic location, net coverage, and malaria incidence at baseline; 1 village within each pair was then randomized to receive the intervention) Number of units: 7:7 Length of follow-up: 12 months (March 1993 to March 1994) Outcome assessment: cross-sectional survey carried out during the peak of the malaria season at baseline and 1 year postintervention. Adjustment: none
Participants	Number of participants: 2450 Inclusion criteria: all inhabitants of the study area. % children under 15 = 51.6%
Interventions	Intervention: community programme for sales and promotion of bed nets, and free net treatment (n = 1418) Insecticide and dosage: permethrin treatment of existing bed nets; target dose 200 mg/m^2

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Kroeger 1995 (Ecuador) (*Continued*)

	Retreatment: not stated Usage: nearly 80% of all existing nets were treated at least once. Control: untreated net (n = 1032). Usage was very high (> 90% coverage)
Outcomes	Outcomes measured: period-prevalence (last 2 weeks or last 4 months) of reported "malaria episodes" assessed during the peak of the malaria season (March to April) Outcome measures were similar to Kroeger 1995 (Colombia).
Notes	Study location: Canton Muisne, on the northern coast of Ecuador EIR: < 1 Malaria transmission: hypoendemic and unstable with marked seasonal variation Main vectors: *Anopheles albimanus* % *P vivax* cases: 51%

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	It was stated that villages were paired and randomly allocated, but randomization programme is not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not possible to blind participants and personnel, but the review authors judge that this lack of blinding was unlikely to have affected the outcome of malaria infection
Blinding of outcome assessment (detection bias) Self-reported fever	High risk	As participants were not blinded, this may introduce bias for the outcome measurement, particularly as the reporting of cases is subject to participants self reporting and recalling over a 4-month period
Blinding of outcome assessment (detection bias) All other outcomes	Low risk	These outcomes were not assessed.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting of attrition to permit judgement
Selective reporting (reporting bias)	Low risk	Outcomes reported are those expected, as they are in line with a series of trials conducted by the same authors across South America

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Kroeger 1995 (Ecuador) (*Continued*)

Other bias	Low risk	Recruitment bias: low risk Baseline imbalance: no significant variation in incidence rate at baseline Loss of clusters: none Incorrect analysis: no adjustment to CIs to account for clustering Comparability with RCTs randomizing individuals: not comparable unless clustering is adjusted for by review authors

Kroeger 1995 (Peru Amazon)

Methods	Study design: cRCT Unit of allocation: village (36 villages were paired according to size, geographic location, net coverage, and malaria incidence at baseline; 1 village within each pair was then randomized to receive the intervention) Number of units: 18:18 Length of follow-up: 12 months (April 1991 to April 1992) Outcome assessment: cross-sectional survey carried out during the peak of the malaria season at baseline and 1 year postintervention
Participants	Number of participants: 5709 Inclusion criteria: all inhabitants of the study area. % children under 15 = 44.9%
Interventions	Intervention: community programme for free net treatment (n = 2993); sales not necessary as usage was already very high Insecticide and dosage: permethrin treatment of existing bed nets; target dose 200 mg/m^2 Retreatment: not stated Usage: nearly 61% of all existing nets treated at least once. Control: untreated net (n = 2716). Usage was very high (95% coverage)
Outcomes	Outcomes measured: period-prevalence (last 2 weeks or last 4 months) of reported "malaria episodes" assessed during April Outcome measures were similar to Kroeger 1995 (Colombia).
Notes	Study location: Tambopata District, Madre de Dios Department in the Amazonas region of Peru EIR: < 1 Malaria transmission: hypoendemic, little seasonality Main vectors: *Anopheles nuneztovari* and *Anopheles rangeli* % *P vivax* cases: 100%

Risk of bias

Bias	Authors' judgement	Support for judgement

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Kroeger 1995 (Peru Amazon) (*Continued*)

Random sequence generation (selection bias)	Unclear risk	It was stated that villages were paired and randomly allocated, but randomization programme is not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not possible to blind participants and personnel, but the review authors judge that this lack of blinding was unlikely to have affected the outcome of malaria infection
Blinding of outcome assessment (detection bias) Self-reported fever	High risk	As participants were not blinded, this may introduce bias for the outcome measurement, particularly as the reporting of cases is subject to participants self reporting and recalling over a 4-month period
Blinding of outcome assessment (detection bias) All other outcomes	Low risk	Other outcomes were not assessed.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting of number randomized or reasons for attrition to permit judgement
Selective reporting (reporting bias)	Low risk	Outcomes reported are those expected, as they are in line with a series of trials conducted by the same authors across South America
Other bias	High risk	Recruitment bias: low risk Baseline imbalance: incidence rate was significantly higher in the intervention group at baseline Loss of clusters: none Incorrect analysis: no adjustment to CIs to account for clustering Comparability with RCTs randomizing individuals: not comparable unless clustering is adjusted for by review authors

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Kroeger 1995 (Peru Coast)

Methods	Study design: cRCT Unit of allocation: village (12 villages were paired according to size, geographic location, net coverage, and malaria incidence at baseline; 1 village within each pair was then randomized to receive the intervention) Number of units: 6:6 Length of follow-up: 2 years (June 1991 to June 1993) Outcome assessment: cross-sectional survey carried out during the peak of the malaria season at baseline, 1 year postintervention, and 2 years postintervention
Participants	Number of participants: 6941 year 1; 6810 year 2 Inclusion criteria: all inhabitants of the study area. % children under 15 = 44.3%
Interventions	Intervention: community programme for sales and promotion of bed nets, and free net treatment (n = 2859) Insecticide and dosage: lambda-cyhalothrin treatment of existing bed nets; target dose 10 to 30 mg/m^2 for the first year and permethrin (500 mg/m^2) for the second year Retreatment: not stated Usage: nearly 60% of all existing nets were treated at least once. Control: untreated net (n = 4082). Usage was very high (96% coverage)
Outcomes	Outcomes measured: period-prevalence (last 2 weeks or last 4 months) of reported "malaria episodes" assessed during the peak of the malaria season (June to July) Outcome measures were similar to Kroeger 1995 (Colombia).
Notes	Study location: Communidad de Catacaos, Piura Department, northern Peru on the Pacific Coast EIR: < 1 Malaria transmission: hypoendemic and unstable with marked seasonal variation Main vectors: *Anopheles albimanus* % *P vivax* cases: 100%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	It was stated that villages were paired and randomly allocated, but randomization programme is not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not possible to blind participants and personnel, but the review authors judge that this lack of blinding was unlikely to have affected the outcome of malaria infection
Blinding of outcome assessment (detection bias) Self-reported fever	High risk	As participants were not blinded, this may introduce bias for the outcome measurement, particularly as the reporting of cases

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Kroeger 1995 (Peru Coast) (*Continued*)

		is subject to participants self reporting and recalling over a 4-month period
Blinding of outcome assessment (detection bias) All other outcomes	Low risk	Other outcomes were not assessed.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting of number randomized or reasons for attrition to permit judgement
Selective reporting (reporting bias)	Low risk	Outcomes reported are those expected, as they are in line with a series of trials conducted by the same authors across South America
Other bias	Low risk	Recruitment bias: low risk Baseline imbalance: no significant difference in incidence rate between intervention groups at baseline Loss of clusters: none Incorrect analysis: no adjustment to CIs to account for clustering Comparability with RCTs randomizing individuals: not comparable unless clustering is adjusted for by review authors

Kroeger 1999

Methods	Study design: cRCT Unit of allocation: village. 12 communities were paired according to size, net coverage, socio-economic characteristics, and malaria incidence at baseline; 1 village within each pair was then randomized to receive the intervention. For the second year, 26 communities (13 pairs) were added to the trial. Number of units: 19:19 (only 10 pairs of clusters were used for the review analysis as the remaining 9 clusters had ITN coverage < 31% in intervention groups) Length of follow-up: 12 months (postintervention study conducted in 1995 for initial 6 pairs and 1996 for following pairs) Outcome assessment: cross-sectional survey carried out during the peak of the malaria season at baseline and 1 year postintervention
Participants	Number of participants: 5041:5815 Inclusion criteria: all inhabitants of the study area
Interventions	Intervention: community programme for sales and promotion of bed nets, and free net treatment (n = 5041) Insecticide and dosage: lambda-cyhalothrin treatment of existing bed nets; target dose 12.5 mg/m^2 Retreatment: not stated

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Kroeger 1999 (*Continued*)

	Usage: 31% to 70% of individuals used an impregnated net. Control: untreated net (n = 5815)
Outcomes	Outcomes measured: period-prevalence (last 4 months) of reported "malaria episodes" assessed during the peak of the malaria season (March to April) Outcome measures were similar to Kroeger 1995 (Colombia).
Notes	Study location: El Viejo Municipio, Department of Chinandega, North East Nicaragua (Pacific Coast) EIR: < 1 Malaria endemicity: hypoendemic Baseline parasite rate in the whole population: 8% Main vector: *Anopheles albimanus* *P vivax* malaria: 99%

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Villages were randomly assigned using random numbers.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not possible to blind participants and personnel, but the review authors judge that this lack of blinding was unlikely to have affected the outcome of malaria infection
Blinding of outcome assessment (detection bias) Self-reported fever	High risk	As participants were not blinded, this may introduce bias for the outcome measurement, particularly as the reporting of cases is subject to participants self reporting and recalling over a 4-month period
Blinding of outcome assessment (detection bias) All other outcomes	Low risk	Other outcomes were not assessed.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting of number randomized or reasons for attrition to permit judgement
Selective reporting (reporting bias)	Low risk	Outcomes reported are those expected, as they are in line with a series of trials conducted by the same authors across South America

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Kroeger 1999 (*Continued*)

Other bias	Low risk	Recruitment bias: low risk Baseline imbalance: no significant variation in incidence rate at baseline Loss of clusters: none Incorrect analysis: no adjustment to CIs to account for clustering Comparability with RCTs randomizing individuals: not comparable unless clustering is adjusted for by review authors

Luxemburger 1994

Methods	Study design: individual RCT Unit of allocation: individual (1 child per household) Number of units: 175:175 Length of follow-up: 6 months (August 1990 to February 1991) Outcome assessment: passive surveillance system through camp clinics and 2 cross-sectional surveys, one after 3 months and one after 6 months at the end of the study, following the peak of the transmission season
Participants	Number of participants: 350 Inclusion criteria: children aged 5 to 14 years in the displaced persons camp. Children living too far from the schools in other small camps were excluded
Interventions	Intervention: bed net (n = 175) Insecticide and dosage: permethrin (500 mg/m^2) Retreatment: not stated Usage: 93% children under net, with 78% used correctly Control: untreated net (n = 175) compliance similar to intervention group. The proportion of households in the village that possessed impregnated nets at baseline was about 22%
Outcomes	Outcomes measured: • Incidence of clinical episodes for both *P falciparum* and *P vivax* • Prevalence of any parasitaemia
Notes	Study location: Shoklo, largest camp for Karen displaced persons on the Thai-Burmese border EIR: low Malaria transmission: unstable Main vectors: *Anopheles dirus* and*Anopheles minimus* (likely main vectors) % *P vivax* cases: 20%; 10% mixed - analysed separately

Risk of bias

Bias	Authors' judgement	Support for judgement

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Luxemburger 1994 (*Continued*)

Random sequence generation (selection bias)	Low risk	Randomization using random numbers table
Allocation concealment (selection bias)	Unclear risk	Allocation concealment process not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were blinded to treated or untreated net.
Blinding of outcome assessment (detection bias) Self-reported fever	Low risk	Participants and outcome assessors were blinded to treated or untreated net
Blinding of outcome assessment (detection bias) All other outcomes	Low risk	Outcome assessors were blinded to treated or untreated net.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss of participants due to children leaving the camp; numbers were balanced across the intervention groups
Selective reporting (reporting bias)	Low risk	All expected outcomes reported.
Other bias	Low risk	Recruitment bias: low risk Baseline imbalance: all children participating in the study were given a treatment before the beginning of the trial

Magris 2007

Methods	Study design: cRCT Unit of allocation: village (paired) Number of units: 9:9 Length of follow-up: 2 years Outcome assessment: continuous active (fortnightly blood smears of all villagers with fever in last 48 hours) and passive (local health centre) case detection was carried out. 2 cross-sectional surveys carried out after intervention (6 months and 2 years) to measure prevalence. Adjustment: adjusted rate ratio and CIs calculated to account for randomization by cluster and to adjust for potential confounding factors including age and sex
Participants	Number of participants: 924 Inclusion criteria: children under 10
Interventions	Intervention: insecticide-treated hammock net (n = 429) Insecticide and dosage: lambda-cyhalothrin (10 mg/$m^{2)}$ Retreatment: every 6 months

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	Usage: not stated Control: placebo-treated hammock net (n = 495)
Outcomes	Outcomes measured: • Malaria prevalence • Malaria incidence
Notes	Study location: Amazon rainforest, Venezuela EIR: not stated Malaria transmission: predominantly low with pockets of intense transmission Main vectors: *Anopheles darlingi* % *P vivax* cases: not stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	1 village in each pair was assigned at random by tossing a coin to the intervention or the control
Allocation concealment (selection bias)	Low risk	Low risk for bias with the above randomization procedure
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were blinded to intervention or control group.
Blinding of outcome assessment (detection bias) Self-reported fever	Low risk	Participants who self reported fever were blinded to intervention or control group. Malaria cases were confirmed by blood smear examination
Blinding of outcome assessment (detection bias) All other outcomes	Low risk	No blinding of outcome assessors described, however the review authors judge that lack of blinding was very unlikely to have impacted the measurement of prevalence through cross-sectional survey and blood smear examination
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to judge risk of attrition bias. 68% of the total population took part in the postintervention prevalence survey, but the number of participants missing from each intervention group is not described, and reason for missing data is not provided
Selective reporting (reporting bias)	Low risk	All expected outcomes reported.

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Magris 2007 (*Continued*)

Other bias	Low risk	Recruitment bias: low risk Baseline imbalance: villages were paired by baseline incidence Loss of clusters: no loss of clusters Incorrect analysis: adjusted Comparability with RCTs randomizing individuals: suitable for comparison

Marbiah 1998

Methods	Study design: cRCT Unit of allocation: village (17 villages were paired according to size, altitude, climate, and presence of a health centre; 1 village in each pair was then randomized to the intervention; children were also randomized individually to either chemoprophylaxis with pyrimethamine/dapsone or placebo. The review analysis focused on the placebo group in order to exclude the effect of chemoprophylaxis) Number of units: 9:9 Length of follow-up: 1 year Outcome assessment: weekly active case detection where each child recruited into the study was visited by a field worker, and if meeting specific criteria a blood smear was examined. Anaemia was assessed through a cross-sectional survey conducted 9 months postintervention Adjustment: to account for clustering, the CIs for the protective efficacies were calculated from the mean and standard error of the log rate ratios of each pair
Participants	Number of participants: 920 Inclusion criteria: children aged 3 months to 6 years
Interventions	Type of intervention: bed net (n = 470) Insecticide and dosage: lambda-cyhalothrin (10 mg/m^2) Retreatment: not stated Usage: not stated Control: no net (n = 450) Co-interventions: children were randomized individually to either chemoprophylaxis with pyrimethamine/dapsone (Maloprim) or placebo. Only the placebo group is included in this analysis
Outcomes	Outcomes measured: incidence of malaria episodes (children aged 3 months to 6 years)
Notes	Study location: 17 villages near the town of Bo, Sierra Leone EIR: 35 Malaria transmission: hyperendemic Main vectors: *Anopheles gambiae* % *P vivax* cases: 0%

Risk of bias

Bias	Authors' judgement	Support for judgement

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Marbiah 1998 (*Continued*)

Random sequence generation (selection bias)	Low risk	Intervention group was randomly allocated by a lottery.
Allocation concealment (selection bias)	Low risk	Low risk with the above randomization process
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not possible to blind participants and personnel, but the review authors judge that this lack of blinding was unlikely to have affected the outcome of malaria infection
Blinding of outcome assessment (detection bias) Self-reported fever	Unclear risk	Children reporting fever during active surveillance had parasitaemia confirmed by blood smear
Blinding of outcome assessment (detection bias) All other outcomes	Low risk	No other outcomes were assessed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All expected outcomes reported.
Other bias	Low risk	Recruitment bias: low risk Baseline imbalance: the pre-intervention incidence rate was not provided, but intervention groups were comparable for pre-intervention mean haematocrit and splenomegaly prevalence Loss of clusters: none Incorrect analysis: adjusted Comparability with RCTs randomizing individuals: suitable for comparison

Moyou-Somo 1995

Methods	Study design: cRCT Unit of allocation: household (40 households with number of people varying from 5 to 25) Number of units: 20:20 Length of follow-up: 12 months (January to December 1992) Outcome assessment: cross-sectional surveys conducted every 2 months. Adjustment: for quarter and age group
Participants	Number of participants: approximately 480 Inclusion criteria: all inhabitants of the study area; children aged 15 and under

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Moyou-Somo 1995 (*Continued*)

Interventions	Intervention: bed net (n = approximately 240) Insecticide and dosage: deltamethrin; target dose 25 mg/m^2 Retreatment: after 6 months Usage: Not described Control: no net (n = approximately 240)
Outcomes	Parasite prevalence
Notes	Study location: 2 villages in Kumba, South West Cameroon: Kossala (high prevalence) and Mbonge Road (low prevalence) EIR: 10 to 20 Malaria transmission: intense and perennial Main vectors: *Anopheles gambiae s.l.* % *P vivax* cases: 0%

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	It was stated that villages were paired and randomly allocated, but randomization programme is not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not possible to blind participants and personnel, however the review authors judge the risk of bias to be low for the outcome of prevalence
Blinding of outcome assessment (detection bias) Self-reported fever	Low risk	This outcome was not assessed.
Blinding of outcome assessment (detection bias) All other outcomes	Low risk	Not described if blood film examiners were blinded to the intervention group. The review authors judge the risk of bias to be low for the outcome of prevalence as the survey was cross-sectional and the measurement is objective
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting of number randomized and number present at each survey to permit judgement
Selective reporting (reporting bias)	Low risk	Outcomes reported are those that would have been expected to have been reported

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Moyou-Somo 1995 (*Continued*)

Other bias	Unclear risk	Recruitment bias: low risk Baseline imbalance: unclear risk; baseline prevalence not reported Loss of clusters: none Incorrect analysis: no adjustment to CIs to account for clustering Comparability with RCTs randomizing individuals: not comparable unless clustering is adjusted for by review authors

Nevill 1996

Methods	Study design: cRCT Unit of allocation: administrative zones. Stratified by north, southeast, and southwest divisions of the study area due to significant differences in preliminary mortality and hospital presentation data Number of units: 28:28 Length of follow-up: 2 years Outcome assessment: paediatric ward surveillance. Blood sample and clinical diagnosis taken. Biannual census; data were supplemented with 6-weekly house-to-house vital registration of births and deaths
Participants	Number of participants: 22,998 Inclusion criteria: children 1 to 59 months
Interventions	Intervention: bed net (n = 11,566) Insecticide and dosage: permethrin suspension (0.5 g/mL) Retreatment: nets dipped again after 6 months Usage: 77% in intervention group; < 1% in control Control: no net (n = 11,432)
Outcomes	Outcomes measured: • Mortality rate • *P falciparum* positive admissions • Severe malaria admissions (defined as confirmed *P falciparum* parasitaemia accompanied by: ○ coma, defined as being unable to localize a painful stimulus (assessed after 1 hour following a seizure or administration of anticonvulsants and after correction of hypoglycaemia); ○ prostration, defined as being unable to breastfeed or sit unassisted; ○ multiple seizures, 2 or more convulsions within 24 hours prior to admission; ○ severe malaria anaemia, a haemoglobin of less than 5.1 g/dL, and an associated parasitaemia greater than 10,000 parasites per microlitre of blood; ○ hyperparasitaemia, more than 20% of red cells infected; ○ death without any of the aforementioned complications but without evidence of an alternative diagnosis.

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Notes	Study location: Kilifi District, Kenya EIR: 10 to 30 Malaria transmission: hyperendemic. Baseline parasite rate in children 1 to 9 years: 49% in the peak season, with seasonal fluctuation Main vectors: *Anopheles gambiae s.l.* complex *P vivax* malaria: 0%

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Intervention allocation by public lottery (information provided by CL)
Allocation concealment (selection bias)	Low risk	Low risk given the above intervention allocation procedure
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not possible to blind participants and personnel, but this was not likely to have introduced bias
Blinding of outcome assessment (detection bias) Self-reported fever	Unclear risk	Incidence was determined from hospital admissions. This would involve self reporting of fever, though cases were confirmed as positive for parasitaemia
Blinding of outcome assessment (detection bias) All other outcomes	Low risk	Unclear if outcome assessors were blinded, but this was not likely to have introduced bias for mortality or severe malaria measurement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Number randomized is based on full population census. The paper provides sufficient confidence that all deaths and hospital attendances are recorded
Selective reporting (reporting bias)	Low risk	All stated outcomes reported.
Other bias	Low risk	Recruitment bias: low risk Baseline imbalance: the pre-intervention differences are controlled for in the adjusted risk ratios Loss of clusters: none Incorrect analysis: adjusted Comparability with RCTs randomizing individuals: suitable for comparison

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Phillips-Howard 2003

Methods	Study design: cRCT Unit of allocation: village (allocation of 221 villages by open lottery; 79 clusters in Asembo, population 55,000; 142 clusters in Gem, population 70,000) Number of units: 113:108 Length of follow-up: 2 years (Asembo: Jan 1997 to Dec 1998; Gem: Jan 1998 to Dec 1999) Outcome assessment: mortality was monitored by a full demographic system with biannual census. Morbidity was monitored with three cross-sectional surveys completed at baseline (Nov 1996), midpoint (Feb to Mar 1998), and the end of the morbidity study (1998). Adjustment: analysis for mortality rates was completed at the village level and so did not need to take clustering into account. Morbidity analysis controlled for clustering with an exchangeable correlation structure assumed for residents within a village
Participants	Number of participants: approximately 18,500 Inclusion criteria: children aged 1 to 59 months who had lived in the study area for at least 1 month
Interventions	Intervention: treated bed nets Insecticide and dosage: permethrin (500 mg/m^2) Retreatment: aimed to retreat bed nets every 6 months. Due to terrorist bombing of the US embassy, retreatment in some villages was delayed in 1998 and 1999. Usage: 66% adherence Control: no net
Outcomes	Outcomes measured: • All-cause mortality (Asembo and Gem) • Prevalence of people that have clinical malaria (Asembo only)
Notes	Study location: Asembo and Gem, in Nyanza Province on the shore of Lake Victoria, Kenya EIR: 60 to 300 Malaria endemicity: holoendemic Main vector: *Anopheles gambiae* and *Anopheles funestus* *P vivax* malaria: 0%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Villages were randomly assigned by public lottery.
Allocation concealment (selection bias)	Low risk	Village representatives chose a sealed envelope detailing their intervention group
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not possible to blind participants and personnel, however the review authors judge this was unlikely to have introduced bias

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Phillips-Howard 2003 (*Continued*)

		to the outcomes of mortality or clinical episodes of malaria
Blinding of outcome assessment (detection bias) Self-reported fever	Low risk	This outcome was not assessed.
Blinding of outcome assessment (detection bias) All other outcomes	Low risk	Outcome assessors were not blinded to intervention status of participants, but the review authors judge this was unlikely to have introduced bias to the measurement of mortality or prevalence through cross-sectional surveys
Incomplete outcome data (attrition bias) All outcomes	High risk	19 of 79 villages in Asembo region excluded from the cross-sectional studies were in the southernmost area of Asembo, because longitudinal surveillance was still ongoing. The reason was unrelated to the intervention group. The study included children aged 1 to 59 months, but only children aged 1 to 3 years were sampled for the morbidity analysis
Selective reporting (reporting bias)	Low risk	Outcomes reported are those detailed in the study protocol.
Other bias	Low risk	Recruitment bias: low risk Baseline imbalance: no significant variation in incidence rate or parasitaemia at baseline Loss of clusters: none Incorrect analysis: adjusted Comparability with RCTs randomizing individuals: suitable for comparison

Rabarison 1995

Methods	Study design: cRCT Unit of allocation: households Number of units: 91 households at baseline (46 intervention households, 45 controls). 78 households at the end of the study (39 intervention households, 39 controls) Length of follow-up (study dates): 2 distinct periods for a total of 13 months (February 1993 to July 1993, and October 1993 to June 1994) Outcome assessment: passive surveillance through medical consultations at Ankazobé (Institut Pasteur)
Participants	Number of participants: 501 at baseline (244 in the intervention group, 257 in the control group). 431 at the end of the study (208 in the intervention group, 223 in the

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Rabarison 1995 (*Continued*)

	control group) Inclusion criteria: households in Ankazobé district II
Interventions	Intervention: curtain nets attached to the doors and windows of bedrooms Insecticide and dosage: deltamethrin (25 mg/m^2) Net retreatment: done 3 times (specific dates not provided) Usage: not described. Likely to be high as nets are fitted by study personnel and then left Control: untreated nets attached to the doors and windows of bedrooms
Outcomes	Outcomes measured: number of clinical episodes (defined as axillary body temperature over 37.5 C° plus parasitaemia > 1500/ μL)
Notes	Study location: Ankazobé (Madagascar), at altitude of 1300 m EIR: < 10 Malaria transmission (perennial, seasonal, etc.): low seasonal transmission. "Stability index" described as <= 2.5 Main vector species: *Anopheles funestus* and *Anopheles gambiae* % *P vivax* cases: 0%

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Houses were drawn by lottery.
Allocation concealment (selection bias)	Low risk	Low risk of bias considering the above allocation procedure
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Single-blind: participants were blinded to the impregnation status of installed curtains
Blinding of outcome assessment (detection bias) Self-reported fever	Low risk	Passive case detection would have depended on self reporting, but as participants were blinded to intervention this was unlikely to have introduced detection bias. Cases were registered only if confirmed positive for parasitaemia
Blinding of outcome assessment (detection bias) All other outcomes	Low risk	Other outcomes were not assessed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss of households was explained as being mainly due to participants relocating following cyclones in February 1994. Loss was balanced between groups

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Rabarison 1995 (*Continued*)

Selective reporting (reporting bias)	Low risk	Expected outcomes are reported, except for data for August 1993 to September 1993, which is likely due to limited cases outside of the rain season
Other bias	Unclear risk	Recruitment bias: low risk Baseline imbalance: unclear risk. Baseline prevalence not reported Loss of clusters: 13 clusters lost due to participants relocating following cyclones. These were balanced in numbers between groups Incorrect analysis: no adjustment to CIs to account for clustering Comparability with RCTs randomizing individuals: not comparable unless clustering is adjusted for by review authors

Rowland 1996

Methods	Study design: individual RCT Unit of allocation: household (random allocation of 192 households after a first random selection of 20% of all households from a census list; the aim of this procedure was to measure the impact of treated nets in a condition of low net usage) Number of units: 97:95 Length of follow-up: 6 months Outcome assessment: prevalence survey using health centre microscopists before study (followed by treatment) and after 6 months. Passive case detection through health centre attendance data
Participants	Number of participants: 2792 Inclusion criteria: chosen from 2 Afghan refugee camps. All ages
Interventions	Type of intervention: bed net (n = 1398) Insecticide and dosage: permethrin (0.5 g/m^2) Retreatment: not stated Usage: 66% 7 nights per week, 82% 3 to 6 nights per week Control: no net (n = 1394)
Outcomes	Outcomes measured: • Incidence of malaria episodes (both *P falciparum* and *P vivax*) • Prevalence of any parasitaemia (both *P falciparum* and *P vivax*)
Notes	Study location: Mardan District, North West Frontier Province, North West Pakistan EIR: low Malaria transmission: unstable; 22% of individuals reported having had malaria in the past year Main vectors: *Anopheles culicifacies and Anopheles stephensi*

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	% *P vivax* cases: 77% of all cases

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Trial families were randomly selected from the total population and then randomly divided into intervention and control groups, but randomization process is not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding was not possible, but the review authors judge that this was unlikely to have impacted the outcome of malaria infection
Blinding of outcome assessment (detection bias) Self-reported fever	Unclear risk	The review authors judge that participant knowledge of their intervention group could have influenced the self reporting of fever
Blinding of outcome assessment (detection bias) All other outcomes	Low risk	No blinding of outcome assessors described, however the review authors judge that a lack of blinding was very unlikely to have impacted the measurement of prevalence through objective tests
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No reason for missing outcome data provided.
Selective reporting (reporting bias)	Low risk	All expected outcomes reported.
Other bias	Low risk	Recruitment bias: low risk Baseline imbalance: the pre-intervention prevalence of *P falciparum* and *P vivax* was comparable between the intervention and control group.

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Sexton 1990

Methods	Study design: cRCT Unit of allocation: household Number of units: 35 treated bed nets: 35 treated curtains: 35 control Length of follow-up: 15 weeks Outcome assessment: all participants given curative treatment at enrolment. New *P falciparum* infections were determined by weekly blood smears from all family members. Only infections occurring > 4 weeks after a treatment were considered new infections
Participants	Number of participants: 481 Inclusion criteria: all ages
Interventions	Intervention: bed nets (n = 166) and curtains (n = 156) Insecticide and dosage: permethrin (0.5 g/m^2) Retreatment: not stated Usage: 70% to 73% Control: no net (n = 159)
Outcomes	Outcomes measured: incidence of parasitaemia
Notes	Study location: Uriri, western Kenya EIR: not stated Malaria transmission: holoendemic. 77% parasitaemia Main vectors: *Anopheles gambiae s.l.* The trial compared treated bed nets, treated curtains, and no nets. As both interventions met the criteria for the review, in the analysis we added the number in the treated bed net group to the number in the treated curtain group to give the total number of cases and weeks at risk in a combined intervention group

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated randomized, but randomization procedure not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not possible to blind participants and personnel, but this was not likely to have introduced bias to the outcome of parasitaemia
Blinding of outcome assessment (detection bias) Self-reported fever	Low risk	The outcome was not reported.
Blinding of outcome assessment (detection bias) All other outcomes	Low risk	Outcome assessors were not blinded to intervention status of participants, but the review authors judge this was unlikely to have introduced bias to the measurement

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Sexton 1990 (*Continued*)

		of parasitaemia as all family members had a blood smear taken and the measurement is objective
Incomplete outcome data (attrition bias) All outcomes	Low risk	No reason given for missing data, but numbers lost were < 5% (5 individuals lost from bed net group, 1 from curtain group, 0 from control group)
Selective reporting (reporting bias)	Low risk	All expected outcomes reported.
Other bias	Unclear risk	Recruitment bias: low risk Baseline imbalance: unclear. All participants received treatment at enrolment, but the baseline prevalence or incidence is not provided Loss of clusters: none Incorrect analysis: no adjustment to CIs to account for clustering Comparability with RCTs randomizing individuals: not comparable unless clustering is adjusted for by review authors

Smithuis 2013

Methods	Study design: cRCT Unit of allocation: village (paired on the basis of geographical location) Number of units: 10:10 Length of follow-up: 1 year Outcome assessment: passive case detection at local health centre. Children were followed up in 2 postintervention cross-sectional surveys: after 5 months and at the end of the study (10 months). Adjustment: cluster adjustment using intraclass correlation coefficient of 0.048, between-cluster variation 0.006, and within-cluster variation 0.12
Participants	Number of participants: 8395 Inclusion criteria: children under 10 years of age
Interventions	Intervention: bed net (n = 4066) Insecticide and dosage: deltamethrin (25 mg/m^2) Retreatment: not stated Usage: not stated Control: no net (n = 4109)
Outcomes	Outcomes measured: • Malaria prevalence • Malaria incidence • Number of deaths

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	• Number of cases of severe malaria
Notes	Study location: Rakhine State, Western Myanmar, in 2 areas: Dabhine and Myothugyi EIR: not stated Malaria transmission: predominantly low with pockets of intense transmission Main vectors: not stated % *P vivax* cases: 52%, and 2% *P falciparum*/*P vivax* mixed

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	1 village was selected from each pair using a computer-generated random number to receive ITNs
Allocation concealment (selection bias)	Low risk	Low risk of bias considering the above allocation procedure
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Impossible to blind implementers or inhabitants to intervention, but this was unlikely to have introduced bias to the outcomes of malaria infection, morbidity, or mortality
Blinding of outcome assessment (detection bias) Self-reported fever	Unclear risk	Incidence was monitored through passive case detection and depended on self reporting of a fever; cases were confirmed by microscopy
Blinding of outcome assessment (detection bias) All other outcomes	Low risk	The outcomes of mortality, severe malaria cases, and parasite prevalence measured through cross-sectional surveys were unlikely to have been influenced by knowledge of intervention allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were balanced across the intervention groups and numbers lost were below 5%; 4.5% of the experimental group and 2.9% of the control group had moved away or were absent for the final follow-up survey. All other participants were accounted for
Selective reporting (reporting bias)	Low risk	All expected outcomes reported.
Other bias	Low risk	Recruitment bias: low risk Baseline imbalance: the pre-intervention prevalence rates were adjusted for Loss of clusters: 2 planned clusters were

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		lost, but this was before randomization Incorrect analysis: adjusted Comparability with RCTs randomizing individuals: suitable for comparison

Snow 1987

Methods	Study design: cRCT Unit of allocation: household (allocation of 110 compounds was done randomly after stratification by 3 levels of "spleen rate": no child with enlarged spleen in household, 1 child, more than 1 child) Number of units: 60:50 Length of follow-up: 6 months (May to November 1987) Outcome assessment: weekly morbidity survey of participants with those reporting a fever having a blood examination, and 2 cross-sectional surveys: 1 before intervention in May 1987 and 1 after 6 months in November, following the peak of the transmission season
Participants	Number of participants: 389 Inclusion criteria: children aged 1 to 9
Interventions	Intervention: bed net (n = 205) Insecticide and dosage: permethrin (500 mg/m^2) Retreatment: not described Usage: not described Control: placebo-treated net (n = 184). The proportion of households in the village that possessed nets at baseline was about 98%
Outcomes	Outcomes measured: • Incidence of new episodes of malaria • Prevalence of any parasitaemia • Number of deaths
Notes	Study location: Katchang, North bank of River Gambia EIR: 10 Malaria transmission: hyperendemic

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomization stated, but process not described.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment process not described.

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Snow 1987 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants blinded to treated or untreated net.
Blinding of outcome assessment (detection bias) Self-reported fever	Low risk	Outcome assessors blinded to treated or untreated net.
Blinding of outcome assessment (detection bias) All other outcomes	Low risk	Outcome assessors blinded to treated or untreated net.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses of participants were explained and equal between groups
Selective reporting (reporting bias)	Low risk	All expected outcomes reported.
Other bias	Low risk	Recruitment bias: low risk Baseline imbalance: low, as intervention groups were stratified by prevalence Loss of clusters: none Incorrect analysis: no adjustment to CIs to account for clustering Comparability with RCTs randomizing individuals: not comparable unless clustering is adjusted for by review authors

Sochantha 2006

Methods	Study design: cRCT Unit of allocation: villages (paired on the basis of baseline prevalence) Number of units: 17:17 Length of follow-up: 10 months Outcome assessment: passive surveillance system with village malaria workers using rapid diagnostic tests (as a proxy measure to estimate malaria incidence), and blood smear cross-sectional survey after 10 months for prevalence assessment Adjustment: used an exchangeable correlation matrix to adjust for clustering
Participants	Number of participants: 10,726 Inclusion criteria: people of all ages
Interventions	Intervention: bed net (n = 6106) Insecticide and dosage: deltamethrin (25 mg/m^2) Retreatment: at end of follow-up period Usage: 87% intervention group Control: no net (n = 4620). 14% of control group reported use of an ITN

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Outcomes	Outcomes measured: • *P falciparum* prevalence • *P falciparum* positive consultation rate (per person per year)
Notes	Study location: Rattanakiri, North East Cambodia EIR: 6.0 Malaria transmission: perennial, with a peak during the rainy season Main vectors: *Anopheles dirus* % *P vivax* cases: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computerized random number generation
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not possible to blind participants and personnel, but this was not likely to have introduced performance bias
Blinding of outcome assessment (detection bias) Self-reported fever	Unclear risk	It is unclear if the passive surveillance system was blinded to intervention status of participants. An objective rapid diagnostic test was used for assessment, but as this was only on participants self reporting a fever, there is the possibility of bias
Blinding of outcome assessment (detection bias) All other outcomes	Low risk	Intervention group was not identified to blood smear examiners for the cross-sectional survey
Incomplete outcome data (attrition bias) All outcomes	Low risk	The intended sample size for the cross-sectional survey is unclear (250 per village, or 80% of population in villages with < 250, though the size of individual villages is not described). However, the number sampled is balanced across intervention groups
Selective reporting (reporting bias)	Low risk	All expected outcomes reported.
Other bias	Low risk	Recruitment bias: low risk Baseline imbalance: the pre-intervention prevalence rates were adjusted for Loss of clusters: 2 planned clusters were lost, but this was before randomization

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Sochantha 2006 (*Continued*)

		Incorrect analysis: adjusted Comparability with RCTs randomizing individuals: unclear

Abbreviations: cRCT: cluster-randomized controlled trial; CI: confidence interval; EIR: entomological inoculation rate; ITN: insecticide-treated net; RCT: randomized controlled trial.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bhatt 2012	The study design is not appropriate as it grouped villages into just three clusters. A single cluster was randomised to each of the ITN, UTN or NN arms
Sahu 2008	The study design is not appropriate as it grouped villages into just three clusters. A single cluster was randomised to each of the ITN, UTN or NN arms
Sharma 2009	The study design is not appropriate as it grouped villages into just three clusters. A single cluster was randomised to each of the ITN, UTN or NN arms
Snow 1988	Comparison was between untreated nets and no nets. No participants received an ITN
Soleimani-Ahmadi 2012	The study design is not appropriate as it grouped villages into just two clusters. A single cluster was randomised to each of the ITN and UTN arms
Thang 2009	The control group is not appropriate. The study assessed the impact of introducing insecticide treated hammocks to forest workers, compared to those not receiving hammocks. However, the participants all lived in villages with a high coverage of ITNs (88.17% in the control arm), and therefore were unsuitable to act as a control
Zaim 1998	Definition of measured outcome described as "incidence of malaria" is unclear. No other epidemiological outcomes were reported

Abbreviations: ITN: insecticide-treated net; NN: no net; UTN: untreated net.

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DATA AND ANALYSES

Comparison 1. Insecticide-treated nets versus no nets

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Child mortality from all causes	5	0	Rate Ratio (Random, 95% CI)	0.83 [0.77, 0.89]
2 *P falciparum* uncomplicated episodes	5	0	Rate Ratio (Random, 95% CI)	0.55 [0.48, 0.64]
3 *P falciparum* uncomplicated episodes (cumulative incidence)	2	0	Risk Ratio (Random, 95% CI)	0.44 [0.31, 0.62]
4 *P vivax* uncomplicated episodes (cumulative incidence)	2	0	Risk Ratio (Random, 95% CI)	0.61 [0.48, 0.77]
5 Any *Plasmodium spp.* uncomplicated episodes	1	0	Rate Ratio (Fixed, 95% CI)	0.50 [0.28, 0.90]
6 *P falciparum* prevalence	6	0	Risk Ratio (Random, 95% CI)	0.83 [0.71, 0.98]
7 *P vivax* prevalence	2	0	Risk Ratio (Random, 95% CI)	1.00 [0.75, 1.34]
8 Severe malaria episodes	2	8175	Rate Ratio (Random, 95% CI)	0.56 [0.38, 0.82]
9 Anaemia (mean packed cell volume)	5	9182	Mean Difference (Random, 95% CI)	1.29 [0.42, 2.16]

Comparison 2. Insecticide-treated nets versus untreated nets

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Child mortality from all causes	2		Rate Ratio (Random, 95% CI)	0.67 [0.36, 1.23]
2 *P falciparum* uncomplicated episodes	5		Rate Ratio (Random, 95% CI)	0.58 [0.44, 0.78]
3 *P vivax* uncomplicated episodes	3		Rate Ratio (Random, 95% CI)	0.73 [0.51, 1.05]
4 *P vivax* uncomplicated episodes (cumulative incidence)	3		Risk Ratio (Random, 95% CI)	0.59 [0.30, 1.18]
5 Any *Plasmodium spp.* uncomplicated episodes (cumulative incidence)	2		Risk Ratio (Random, 95% CI)	0.47 [0.17, 1.28]
6 *P falciparum* prevalence	3		Risk Ratio (Random, 95% CI)	0.91 [0.78, 1.05]
7 *P vivax* prevalence	1		Risk Ratio (Fixed, 95% CI)	0.68 [0.25, 1.85]
8 Any *Plasmodium spp.* prevalence	1		Risk Ratio (Fixed, 95% CI)	0.17 [0.05, 0.53]
9 Anaemia (mean packed cell volume)	2		Mean Difference (Random, 95% CI)	0.48 [-0.54, 1.50]

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Analysis 1.1. Comparison 1 Insecticide-treated nets versus no nets, Outcome 1 Child mortality from all causes.

Review: Insecticide-treated nets for preventing malaria

Comparison: 1 Insecticide-treated nets versus no nets

Outcome: 1 Child mortality from all causes

Study or subgroup	Favours ITN N	NN N	log [Rate Ratio] (SE)	Rate Ratio IV,Random,95% CI	Weight	Rate Ratio IV,Random,95% CI
Nevill 1996	0	0	-0.3567 (0.1419)		6.4 %	0.70 [0.53, 0.92]
Binka 1996	0	0	-0.1863 (0.0943)		14.6 %	0.83 [0.69, 1.00]
Phillips-Howard 2003	0	0	-0.1744 (0.0444)		65.7 %	0.84 [0.77, 0.92]
Halbluetzel 1996	0	0	-0.1625 (0.0991)		13.2 %	0.85 [0.70, 1.03]
Smithuis 2013	0	0	0.2729 (1.3625)		0.1 %	1.31 [0.09, 18.98]
Total (95% CI)	**0**	**0**			**100.0 %**	**0.83 [0.77, 0.89]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.69$, df = 4 (P = 0.79); $I^2 = 0.0\%$

Test for overall effect: Z = 5.17 (P < 0.00001)

Test for subgroup differences: Not applicable

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Analysis 1.2. Comparison 1 Insecticide-treated nets versus no nets, Outcome 2 *P falciparum* uncomplicated episodes.

Review: Insecticide-treated nets for preventing malaria

Comparison: 1 Insecticide-treated nets versus no nets

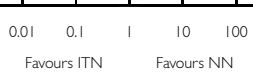
Outcome: 2 *P falciparum* uncomplicated episodes

Study or subgroup	Experimental N	Control N	log [Rate Ratio] (SE)	Rate Ratio IV,Random,95% CI	Weight	Rate Ratio IV,Random,95% CI
Henry 2005 (1)	0	0	-0.844 (0.2767)		7.6 %	0.43 [0.25, 0.74]
Marbiah 1998	0	0	-0.6757 (0.1302)		34.5 %	0.51 [0.39, 0.66]
Nevill 1996	0	0	-0.5447 (0.1527)		25.1 %	0.58 [0.43, 0.78]
Sexton 1990	0	0	-0.5703 (0.1697)		20.3 %	0.57 [0.41, 0.79]
Sochantha 2006 (2)	0	0	-0.3285 (0.2176)		12.4 %	0.72 [0.47, 1.10]
Total (95% CI)	**0**	**0**			**100.0 %**	**0.55 [0.48, 0.64]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.82$, df = 4 (P = 0.59); $I^2 = 0.0\%$

Test for overall effect: Z = 7.73 (P < 0.00001)

Test for subgroup differences: Not applicable



(1) !'' Henry 2005 study's primary vector species (*An. gambiae ss*) was strongly resistant to pyrethroids; *kdr* allelic frequency of ~90%

(2) Sochantha 2006 study was conducted in a high transmission setting in Cambodia (EIR = 6.0)

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Analysis 1.3. Comparison 1 Insecticide-treated nets versus no nets, Outcome 3 *P falciparum* uncomplicated episodes (cumulative incidence).

Review: Insecticide-treated nets for preventing malaria

Comparison: 1 Insecticide-treated nets versus no nets

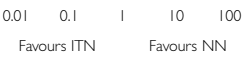
Outcome: 3 *P falciparum* uncomplicated episodes (cumulative incidence)

Study or subgroup	ITN N	NN N	log [Risk Ratio] (SE)	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Rowland 1996	0	0	-0.9577 (0.2018)		66.1 %	0.38 [0.26, 0.57]
Smithuis 2013	0	0	-0.5841 (0.2927)		33.9 %	0.56 [0.31, 0.99]
Total (95% CI)	**0**	**0**			**100.0 %**	**0.44 [0.31, 0.62]**

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 1.10$, df = 1 (P = 0.29); $I^2 = 9\%$

Test for overall effect: Z = 4.70 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1 Insecticide-treated nets versus no nets, Outcome 4 *P vivax* uncomplicated episodes (cumulative incidence).

Review: Insecticide-treated nets for preventing malaria

Comparison: 1 Insecticide-treated nets versus no nets

Outcome: 4 *P vivax* uncomplicated episodes (cumulative incidence)

Study or subgroup	ITN N	NN N	log [Risk Ratio] (SE)	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Rowland 1996	0	0	-0.5443 (0.1094)		84.3 %	0.58 [0.47, 0.72]
Smithuis 2013	0	0	-0.2201 (0.29)		15.7 %	0.80 [0.45, 1.42]
Total (95% CI)	**0**	**0**			**100.0 %**	**0.61 [0.48, 0.77]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.09$, df = 1 (P = 0.30); $I^2 = 9\%$

Test for overall effect: Z = 4.19 (P = 0.000028)

Test for subgroup differences: Not applicable

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Analysis 1.5. Comparison 1 Insecticide-treated nets versus no nets, Outcome 5 Any *Plasmodium spp.* uncomplicated episodes.

Review: Insecticide-treated nets for preventing malaria

Comparison: 1 Insecticide-treated nets versus no nets

Outcome: 5 Any *Plasmodium spp.* uncomplicated episodes

Study or subgroup	ITN N	NN N	log [Rate Ratio] (SE)	Rate Ratio IV,Fixed,95% CI	Weight	Rate Ratio IV,Fixed,95% CI
Smithuis 2013	0	0	-0.6892 (0.2995)		100.0 %	0.50 [0.28, 0.90]
Total (95% CI)	**0**	**0**			**100.0 %**	**0.50 [0.28, 0.90]**

Heterogeneity: not applicable

Test for overall effect: Z = 2.30 (P = 0.021)

Test for subgroup differences: Not applicable

Analysis 1.6. Comparison 1 Insecticide-treated nets versus no nets, Outcome 6 *P falciparum* prevalence.

Review: Insecticide-treated nets for preventing malaria

Comparison: 1 Insecticide-treated nets versus no nets

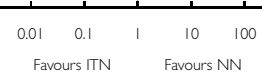
Outcome: 6 *P falciparum* prevalence

Study or subgroup	ITN N	NN N	log [Risk Ratio] (SE)	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Rowland 1996	0	0	-0.5526 (0.2592)		10.0 %	0.58 [0.35, 0.96]
Moyou-Somo 1995	0	0	-0.348 (0.305)		7.2 %	0.71 [0.39, 1.28]
Smithuis 2013	0	0	-0.3066 (0.4627)		3.1 %	0.74 [0.30, 1.82]
Fraser-Hurt 1999	0	0	-0.2963 (0.1637)		25.0 %	0.74 [0.54, 1.02]
Sochantha 2006 (1)	0	0	-0.0943 (0.1717)		22.8 %	0.91 [0.65, 1.27]
Phillips-Howard 2003	0	0	0 (0.1451)		31.9 %	1.00 [0.75, 1.33]
Total (95% CI)	**0**	**0**			**100.0 %**	**0.83 [0.71, 0.98]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 4.73$, df = 5 (P = 0.45); $I^2 = 0.0\%$

Test for overall effect: Z = 2.27 (P = 0.024)

Test for subgroup differences: Not applicable



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(1) Sochantha 2006 study was conducted in a high transmission setting in Cambodia (EIR = 6.0)

Analysis 1.7. Comparison 1 Insecticide-treated nets versus no nets, Outcome 7 *P vivax* prevalence.

Review: Insecticide-treated nets for preventing malaria

Comparison: 1 Insecticide-treated nets versus no nets

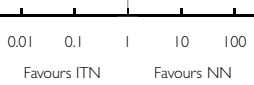
Outcome: 7 *P vivax* prevalence

Study or subgroup	ITN N	NN N	log [Risk Ratio] (SE)	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Rowland 1996	0	0	0.0916 (0.1777)		70.1 %	1.10 [0.77, 1.55]
Smithuis 2013	0	0	-0.2066 (0.2719)		29.9 %	0.81 [0.48, 1.39]
Total (95% CI)	**0**	**0**			**100.0 %**	**1.00 [0.75, 1.34]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.84$, df = 1 (P = 0.36); $I^2 = 0.0\%$

Test for overall effect: Z = 0.02 (P = 0.99)

Test for subgroup differences: Not applicable



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Analysis 1.8. Comparison 1 Insecticide-treated nets versus no nets, Outcome 8 Severe malaria episodes.

Review: Insecticide-treated nets for preventing malaria

Comparison: 1 Insecticide-treated nets versus no nets

Outcome: 8 Severe malaria episodes

Study or subgroup	ITN N	NN N	log [Rate Ratio] (SE)	Rate Ratio IV,Random,95% CI	Weight	Rate Ratio IV,Random,95% CI
Nevill 1996	0	0	-0.5798 (0.1978)		99.7 %	0.56 [0.38, 0.83]
Smithuis 2013	4066	4109	-1.0881 (3.7492)		0.3 %	0.34 [0.00, 523.32]
Total (95% CI)	**4066**	**4109**			**100.0 %**	**0.56 [0.38, 0.82]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.02$, df = 1 (P = 0.89); $I^2 = 0.0\%$

Test for overall effect: Z = 2.94 (P = 0.0033)

Test for subgroup differences: Not applicable

Analysis 1.9. Comparison 1 Insecticide-treated nets versus no nets, Outcome 9 Anaemia (mean packed cell volume).

Review: Insecticide-treated nets for preventing malaria

Comparison: 1 Insecticide-treated nets versus no nets

Outcome: 9 Anaemia (mean packed cell volume)

Study or subgroup	Experimental N	Control N	Mean Difference (SE)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Fraser-Hurt 1999	60	60	1.5 (0.352)		30.0 %	1.50 [0.81, 2.19]
Henry 2005	83	72	2 (1.4102)		7.8 %	2.00 [-0.76, 4.76]
Marbiah 1998	470	450	5.4 (2.3504)		3.3 %	5.40 [0.79, 10.01]
Phillips-Howard 2003	0	0	1.5 (0.4592)		26.5 %	1.50 [0.60, 2.40]
Smithuis 2013	3953	4034	0.33 (0.2776)		32.3 %	0.33 [-0.21, 0.87]
Total (95% CI)	**4566**	**4616**			**100.0 %**	**1.29 [0.42, 2.16]**

Heterogeneity: $Tau^2 = 0.54$; $Chi^2 = 13.00$, df = 4 (P = 0.01); $I^2 = 69\%$

Test for overall effect: Z = 2.89 (P = 0.0038)

Test for subgroup differences: Not applicable

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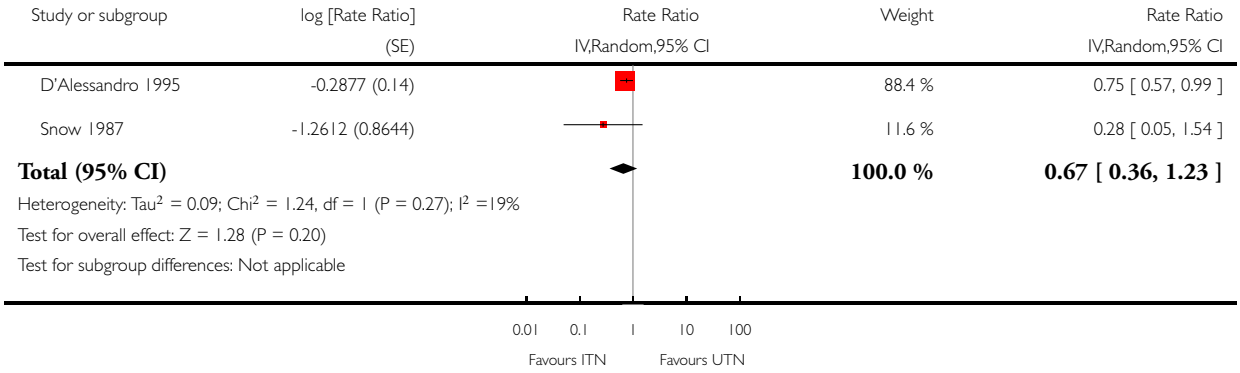
Analysis 2.1. Comparison 2 Insecticide-treated nets versus untreated nets, Outcome 1 Child mortality from all causes.

Review: Insecticide-treated nets for preventing malaria

Comparison: 2 Insecticide-treated nets versus untreated nets

Outcome: 1 Child mortality from all causes



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Analysis 2.2. Comparison 2 Insecticide-treated nets versus untreated nets, Outcome 2 *P falciparum* uncomplicated episodes.

Review: Insecticide-treated nets for preventing malaria

Comparison: 2 Insecticide-treated nets versus untreated nets

Outcome: 2 *P falciparum* uncomplicated episodes

Study or subgroup	log [Rate Ratio] (SE)	Rate Ratio IV,Random,95% CI	Weight	Rate Ratio IV,Random,95% CI
Kamol-Ratanakul 1992	-0.6249 (0.3025)		13.5 %	0.54 [0.30, 0.97]
Luxemburger 1994	-0.5401 (0.2187)		18.4 %	0.58 [0.38, 0.89]
Magris 2007	-0.7765 (0.0713)		28.6 %	0.46 [0.40, 0.53]
Rabarison 1995	-0.2143 (0.1232)		25.3 %	0.81 [0.63, 1.03]
Snow 1987	-0.5534 (0.2859)		14.3 %	0.57 [0.33, 1.01]
Total (95% CI)			**100.0 %**	**0.58 [0.44, 0.78]**

Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 15.84$, df = 4 (P = 0.003); $I^2 = 75\%$

Test for overall effect: Z = 3.63 (P = 0.00029)

Test for subgroup differences: Not applicable

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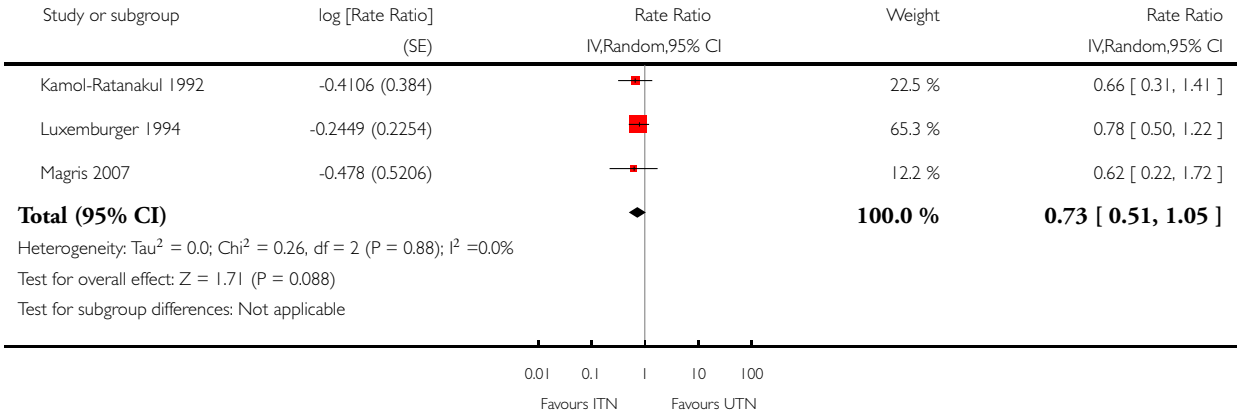
Analysis 2.3. Comparison 2 Insecticide-treated nets versus untreated nets, Outcome 3 *P vivax* uncomplicated episodes.

Review: Insecticide-treated nets for preventing malaria

Comparison: 2 Insecticide-treated nets versus untreated nets

Outcome: 3 *P vivax* uncomplicated episodes

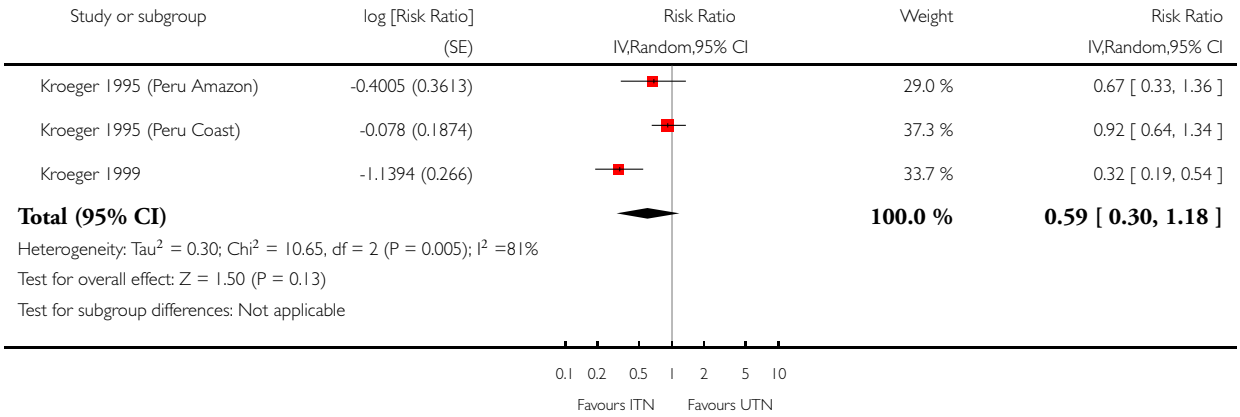


Analysis 2.4. Comparison 2 Insecticide-treated nets versus untreated nets, Outcome 4 *P vivax* uncomplicated episodes (cumulative incidence).

Review: Insecticide-treated nets for preventing malaria

Comparison: 2 Insecticide-treated nets versus untreated nets

Outcome: 4 *P vivax* uncomplicated episodes (cumulative incidence)



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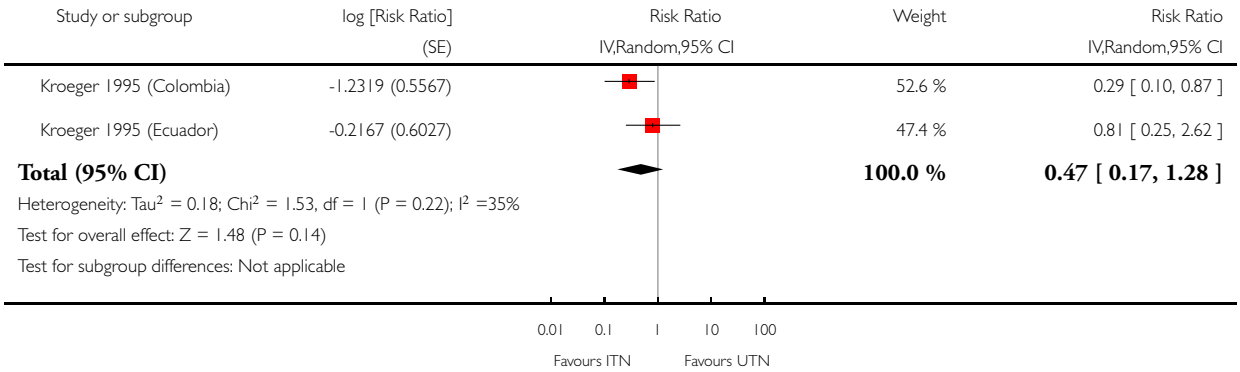
Analysis 2.5. Comparison 2 Insecticide-treated nets versus untreated nets, Outcome 5 Any *Plasmodium spp.* uncomplicated episodes (cumulative incidence).

Review: Insecticide-treated nets for preventing malaria

Comparison: 2 Insecticide-treated nets versus untreated nets

Outcome: 5 Any *Plasmodium spp.* uncomplicated episodes (cumulative incidence)



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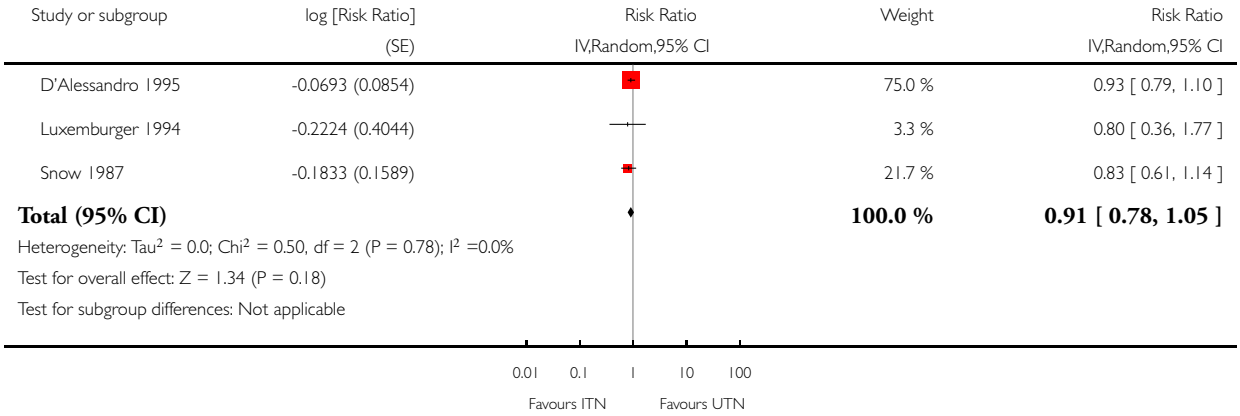
Analysis 2.6. Comparison 2 Insecticide-treated nets versus untreated nets, Outcome 6 *P falciparum* prevalence.

Review: Insecticide-treated nets for preventing malaria

Comparison: 2 Insecticide-treated nets versus untreated nets

Outcome: 6 *P falciparum* prevalence

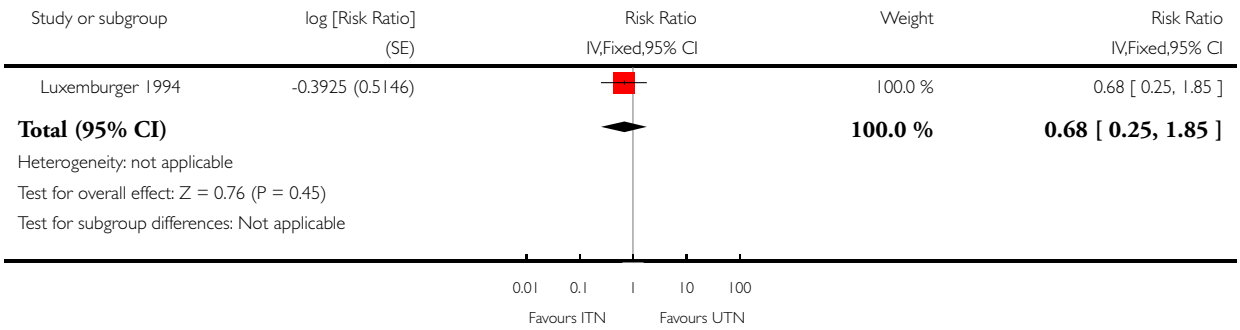


Analysis 2.7. Comparison 2 Insecticide-treated nets versus untreated nets, Outcome 7 *P vivax* prevalence.

Review: Insecticide-treated nets for preventing malaria

Comparison: 2 Insecticide-treated nets versus untreated nets

Outcome: 7 *P vivax* prevalence



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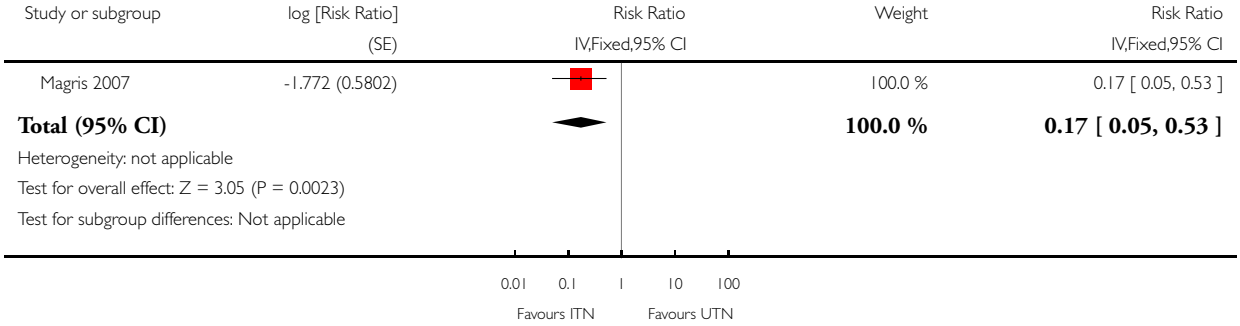
Analysis 2.8. Comparison 2 Insecticide-treated nets versus untreated nets, Outcome 8 Any *Plasmodium spp.* prevalence.

Review: Insecticide-treated nets for preventing malaria

Comparison: 2 Insecticide-treated nets versus untreated nets

Outcome: 8 Any *Plasmodium spp.* prevalence

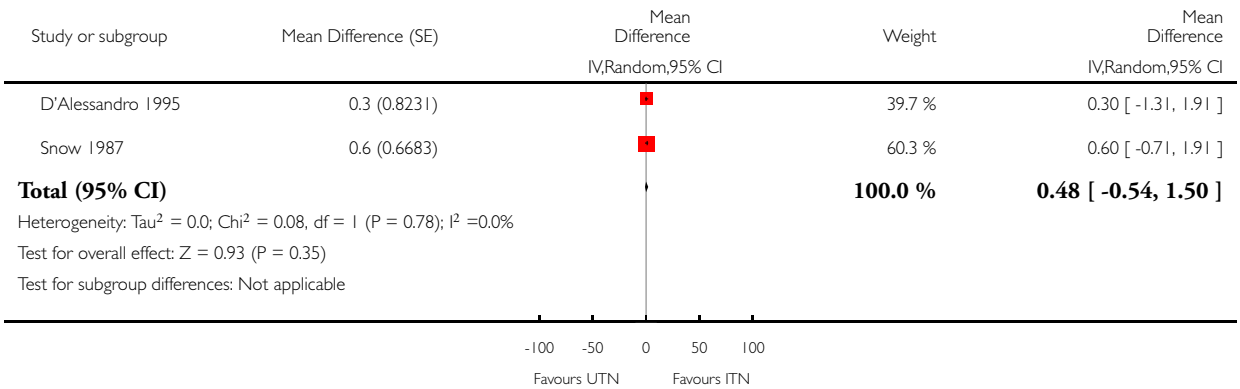


Analysis 2.9. Comparison 2 Insecticide-treated nets versus untreated nets, Outcome 9 Anaemia (mean packed cell volume).

Review: Insecticide-treated nets for preventing malaria

Comparison: 2 Insecticide-treated nets versus untreated nets

Outcome: 9 Anaemia (mean packed cell volume)



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APPENDICES

Appendix 1. Inclusion criteria for studies in the previous update of this review

Study designs	Individual randomized controlled trials (RCTs) and cluster RCTs
Participants	Children and adults living in rural and urban malarious areas Excluded: trials examining only pregnant women and trials examining only soldiers or travellers, because they are not representative of the general population
Interventions	Bed nets or curtains treated with a synthetic pyrethroid insecticide at a minimum target impregnation dose of: • 200 mg/m^2 permethrin or etofenprox; • 30 mg/m^2 cyfluthrin; • 20 mg/m^2 alpha-cypermethrin; • 10 mg/m^2 deltamethrin/lambda-cyhalothrin. No distinction was made between insecticide-treated bed nets and door/window/eave/wall curtains, which were assumed to have approximately the same impact
Comparators	Untreated net or no net
Outcomes	• Child mortality from all causes: measured using protective efficacy and rate difference. • Malaria-specific child mortality: measured using "verbal autopsy" reports that fulfil standard clinical criteria for a probable malaria death (Snow 1992; Todd 1994). • Severe disease: measured using site-specific definitions based on World Health Organization guidelines, WHO 1990, and on Marsh 1995. The definition included *Plasmodium falciparum* parasitaemia. Cerebral malaria was defined as coma or prostration and/or multiple seizures. The cut-off for severe, life-threatening anaemia was set at 5.1 g/L (WHO 1990). • Uncomplicated clinical episodes: measured using site-specific definitions, including measured or reported fever, with or without parasitological confirmation. Measurements were usually done in the frame of prospective longitudinal studies, but we also considered trials using validated retrospective assessments in the frame of cross-sectional surveys. In areas with entomological inoculation rates below 1 (unstable malaria), we considered *P falciparum* and *P vivax* episodes separately. • Parasite prevalence: parasite prevalence due to *P falciparum* and *P vivax* was obtained using the site-specific method for estimating parasitaemia, that is usually thick or thin blood smears or both. When more than one survey was done, the reported prevalence result is the average prevalence of all the surveys.

Appendix 2. Search strategy

Cochrane Central Register of Controlled Trials

Issue 4 of 12, April 2018:
ID Search
#1 MeSH descriptor: [Malaria] explode all trees
#2 malaria:ti,ab,kw (Word variations have been searched)
#3 anopheles :ti, ab, kw
#4 MeSH descriptor: [Anopheles] explode all trees
#5 mosquito* :ti, ab, kw
#6 #1 or #2 or #3 or #4 or #5

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#7 (Net* or bednet* or ITN* or LLIN* or “Insecticide-Treated Bednet*” or “Insecticide-Treated net*”ti, ab,kw
#8 MeSH descriptor: Insecticide-Treated Bednets
#9 (Olyset* or PermaNet* or Veeralin):ti, ab, kw
#10 #7 or #8 or #9
#11 #6 and #10 with Publication Year from 2003 to 2018

PubMed (MEDLINE)

Search	Query
#16	Search (#11) AND #15
#15	Search (#12) OR #13 OR #14 Filters: Publication date from 2003/01/01
#14	Search “drug therapy” [Subheading]
#13	Search “Randomized Controlled Trial” [Publication Type] OR “Controlled Clinical Trial” [Publication Type]
#12	Search randomized or placebo or randomly or trial or groups Field: Title/Abstract
#11	Search (#9) AND #10 Filters: Publication date from 2003/01/01;
#10	Search (#6) OR #7 OR #8 Publication date from 2003/01/01;
#9	Search (#1) OR #2 OR #3 OR #4 OR #5 Filters: Publication date from 2003/01/01;
#8	Search Olyset* or PermaNet* or Veeralin Field: Title/Abstract
#7	Search bednet* or net* or ITN* or LLIN* or curtain* or “insecticide-treated net*” or “insecticide-treated bednet*” Field: Title/Abstract
#6	Search (“Insecticide-Treated Bednets”[Mesh]) OR “Mosquito Nets”[Mesh]
#5	Search malaria Field: Title/Abstract
#4	Search “Plasmodium”[Mesh]
#3	Search “Malaria”[Mesh]
#2	Search mosquito Field: Title/Abstract
#1	Search “Anopheles”[Mesh]

Embase

1 (malaria* or plasmodium or anopheles).mp.
2 insecticide-treated nets.mp. or insecticide treated net/
3 (bednet* or net* or ITN* or LLIN* or curtain*).ab. or (bednet* or net* or ITN* or LLIN* or curtain*).ti.

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4 (Olyset* or PermaNet* or Veeralin).ab. or (Olyset* or PermaNet* or Veeralin).ti.
5 2 or 3 or 4
7 1 and 5
8 limit 7 to yr="2003 -Current"
9 randomized controlled trial/ or controlled clinical trial/
10 ((randomi?ed) or (singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)) .ab. or ((randomi?ed) or (singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).ti.
11 9 or 10
12 8 and 11

LILACS

(tw:(bednets OR nets OR itn)) AND (tw:(malaria OR mosquito OR anopheles)) AND (tw:(randomized OR controlled OR trial OR comparison OR compared))

ClinicalTrials.gov and WHO ICTRP

insecticide treated nets and Malaria

Appendix 3. Revised protocol for review update (2018)

Protocol section	Refreshed protocol
Background	• We updated information in the background to reflect the changes in global malaria distribution and its control since the previous update. • We included further information on insecticide resistance and the need to consider this when evaluating the effectiveness of ITNs.
Methods	• The primary objective of the review, to assess the impact of ITNs on mortality and malarial illness, remains relevant. The original PICO remains relevant. • In the previous review, mortality data was age-standardized across each included study by extracting only the number of deaths and total number of participants within a high-risk age group of 1 to 59 months. To avoid the exclusion of potentially useful information, we planned to extract mortality data for children of all ages who participated in the included studies. However, we also planned to calculate the baseline risk in the high-risk age group by extracting the number of deaths and total number of children aged 1 to 59 months. From this we estimated the impact of ITNs on mortality in the high-risk age group. • For the secondary outcomes, summary risk and rate ratios were previously presented without CIs, as cluster-adjusted CIs were not available for all trials. If an included cRCT did not adjust for clustering, we planned to adjust the data using an imputed design effect. The cRCTs were then meta-analysed, and cluster-adjusted CIs for each outcome were provided. • We excluded the outcomes of splenomegaly, high parasitaemia, and anthropometric measures, which were considered in the previous review (Lengeler 2004), as we did not consider them priority outcomes at the time of this update. • We updated our approach to assessing risk of bias, and used the standardized Cochrane's 'Risk of bias' tool. For each included cRCT we also assessed five additional criteria relating specifically to cRCTs. • We included all relevant trials in the meta-analysis regardless of the local area's transmission intensity, and intended to subgroup between stable and unstable transmission only if we identified substantial heterogeneity. • We assessed the certainty of the evidence using the GRADE approach.

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WHAT'S NEW

Date	Event	Description
6 November 2018	New citation required but conclusions have not changed	We excluded the outcomes of splenomegaly, high parasitaemia, and anthropometric measures, which were considered in the previous review (Lengeler 2004). In this update we extracted mortality data for children of all ages who participated in the included studies. However, we also calculated the baseline risk in the high-risk age group by extracting the number of deaths and total number of children aged 1 to 59 months. From this we estimated the impact of ITNs on mortality in the high-risk age group For the secondary outcomes, summary risk and rate ratios were previously presented without CIs, as cluster-adjusted CIs were not available for all trials. If an included cRCT did not adjust for clustering, we adjusted the data using an imputed design effect. The cRCTs were then meta-analysed, and cluster-adjusted CIs for each outcome were provided
6 November 2018	New search has been performed	This is an update of the Lengeler 2004 review. We performed a literature search update, and included three articles, reporting three new trials, and five new articles relating to trials included in the previous update. We excluded two trials included in the previous version of the review. We assessed the certainty of the evidence using the GRADE approach. We assessed the risk of bias for each included study in this update using Cochrane's 'Risk of bias' tool; for each included cRCT, we also assessed five additional criteria relating specifically to cRCTs

HISTORY

Protocol first published: Issue 1, 1995

Review first published: Issue 3, 1998

Date	Event	Description
18 August 2008	Amended	Converted to new review format with minor editing.
19 January 2004	New citation required but conclusions have not changed	Issue 2, 2004 This is a major update with a revision of the text, tables, and results.

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(*Continued*)

		- An additional 16 trials have been identified and reviewed, of which 4 were included. - The sensitivity analysis (with group 2 trials) has been removed to clarify the main results. - The literature in all sections and especially background and discussion has been updated. - Overall mortality results have been entered with the reverse variance function in order to present confidence intervals adjusted for clustering
12 January 2004	New search has been performed	Minor update.
23 October 2003	New search has been performed	New studies sought but none found.
21 January 2003	New search has been performed	New studies found and included or excluded.

CONTRIBUTIONS OF AUTHORS

JP conducted the search and screened studies published between 2004 and 18 April 2018; rescreened studies from the previous review against the new inclusion criteria; extracted study characteristics and outcome data from all included studies; assessed the risk of bias using new tools; conducted the meta-analyses using cluster-adjusted data and graded the certainty of the evidence; and prepared the final manuscript.

MR provided statistical support throughout.

CL conducted the original search and screened all studies up to 2004. For the previous review, CL extracted information from the included studies; assessed risk of bias; conducted analyses; and prepared the manuscript following the previous review's methodology. For this review update, CL provided guidance on data extraction; conducting the GRADE analysis; and assisted with the manuscript preparation.

All review authors have read and approved the final manuscript.

DECLARATIONS OF INTEREST

JP has no known conflicts of interest.

MR has no known conflicts of interest.

CL has no known conflicts of interest.

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Project number 300342-104

- World Health Organization (WHO), Switzerland.

WHO Global Malaria Programme Agreement for Performance of Work (APW) Grant 2017 (number 709319)

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

N/A.

Differences between revised protocol and review update

Before conducting the review update, the review author team revised the original published protocol, Lengeler 1995 (see Appendix 3). We had intended to perform two pre-specified subgroup analyses: one that subgrouped according to malaria transmission stability and a second that subgrouped cRCTs from individual RCTs. However, we did not perform either analysis as we only detected substantial heterogeneity in one outcome, for which the contributing studies were all cRCTs in unstable malaria transmission settings. Subgrouping would therefore not have provided any insight into the heterogeneity. Otherwise, we followed the methods specified in the revised protocol (Appendix 3) and Methods section.

INDEX TERMS

Medical Subject Headings (MeSH)

*Bedding and Linens; Insecticides [*administration & dosage]; Malaria [*prevention & control]; Malaria, Falciparum [prevention & control]; Malaria, Vivax [prevention & control]; Mosquito Control [*methods]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Male; Pregnancy

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