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Indoor residual spraying for preventing malaria in communities using insecticide-treated nets (Review)

Pryce J, Medley N, Choi L

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Cochrane Database of Systematic Reviews 2022, Issue 1. Art. No.: CD012688.
DOI: 10.1002/14651858.CD012688.pub3.

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TABLE OF CONTENTS

[Intervention Review]

Indoor residual spraying for preventing malaria in communities using insecticide-treated nets

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Editorial group: Cochrane Infectious Diseases Group.
Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 1, 2022.

Citation: Pryce J, Medley N, Choi L. Indoor residual spraying for preventing malaria in communities using insecticide-treated nets. *Cochrane Database of Systematic Reviews* 2022, Issue 1. Art. No.: CD012688. DOI: 10.1002/14651858.CD012688.pub3.

ABSTRACT

Background

Insecticide-treated nets (ITNs) and indoor residual spraying (IRS) are used to prevent malaria transmission. Both interventions use insecticides to kill mosquitoes that bite and rest indoors. Adding IRS to ITNs may improve malaria control simply because two interventions can be better than one. Furthermore, IRS may improve malaria control where ITNs are failing due to insecticide resistance. Pyrethroid insecticides are the predominant class of insecticide used for ITNs, as they are more safe than other insecticide classes when in prolonged contact with human skin. While many mosquito populations have developed some resistance to pyrethroid insecticides, a wider range of insecticides can be used for IRS. This review is an update of the previous Cochrane 2019 edition.

Objectives

To summarize the effect on malaria of additionally implementing IRS, using non-pyrethroid-like or pyrethroid-like insecticides, in communities currently using ITNs.

Search methods

We searched the Cochrane Infectious Diseases Group Specialized Register; CENTRAL; MEDLINE; and five other databases for records from 1 January 2000 to 8 November 2021, on the basis that ITN programmes did not begin to be implemented as policy before the year 2000.

Selection criteria

We included cluster-randomized controlled trials (cRCTs), interrupted time series (ITS), or controlled before-after studies (CBAs) comparing IRS plus ITNs with ITNs alone. We included studies with at least 50% ITN ownership (defined as the proportion of households owning one or more ITN) in both study arms.

Data collection and analysis

Two review authors independently assessed studies for eligibility, analyzed risk of bias, and extracted data. We used risk ratio (RR) and 95% confidence intervals (CI). We stratified by type of insecticide, 'pyrethroid-like' and 'non-pyrethroid-like'; the latter could improve malaria control better than adding IRS insecticides that have the same way of working as the insecticide on ITNs ('pyrethroid-like'). We used subgroup analysis of ITN usage in the studies to explore heterogeneity. We assessed the certainty of evidence using the GRADE approach.

Main results

Eight cRCTs (10 comparisons), one CBA, and one ITS study, all conducted since 2008 in sub-Saharan Africa, met our inclusion criteria. The primary vectors in all sites were mosquitoes belonging to the *Anopheles gambiae s.l.* complex species; five studies in Benin, Mozambique, Ghana, Sudan, and Tanzania also reported the vector *Anopheles funestus*. Five cRCTs and both quasi-experimental design studies used insecticides with targets different to pyrethroids (two used bendiocarb, three used pirimiphos-methyl, and one used propoxur. Each of these studies were conducted in areas where the vectors were described as resistant or highly resistant to pyrethroids. Two cRCTs used dichloro-diphenyl-trichlorethane (DDT), an insecticide with the same target as pyrethroids. The remaining cRCT used both types of insecticide (pyrethroid deltamethrin in the first year, switching to bendiocarb for the second year).

Indoor residual spraying using 'non-pyrethroid-like' insecticides

Six studies were included (four cRCTs, one CBA, and one ITS). Our main analysis for prevalence excluded a study at high risk of bias due to repeated sampling of the same population. This risk did not apply to other outcomes. Overall, the addition of IRS reduced malaria parasite prevalence (RR 0.61, 95% CI 0.42 to 0.88; 4 cRCTs, 16,394 participants; high-certainty evidence). IRS may also reduce malaria incidence on average (rate ratio 0.86, 95% CI 0.61 to 1.23; 4 cRCTs, 323,631 child-years; low-certainty evidence) but the effect was absent in two studies. Subgroup analyses did not explain the qualitative heterogeneity between studies. One cRCT reported no effect on malaria incidence or parasite prevalence in the first year, when a pyrethroid-like insecticide was used for IRS, but showed an effect on both outcomes in the second year, when a non-pyrethroid-like IRS was used.

The addition of IRS may also reduce anaemia prevalence (RR 0.71, 95% CI 0.38 to 1.31; 3 cRCTs, 4288 participants; low-certainty evidence). Four cRCTs reported the impact of IRS on entomological inoculation rate (EIR), with variable results; overall, we do not know if IRS had any effect on the EIR in communities using ITNs (very low-certainty evidence). Studies also reported the adult mosquito density and the sporozoite rate, but we could not summarize or pool these entomological outcomes due to differences in the reported data. Three studies measured the prevalence of pyrethroid resistance before and after IRS being introduced: there was no difference detected, but these data are limited.

Indoor residual spraying using 'pyrethroid-like' insecticides

Adding IRS using a pyrethroid-like insecticide did not appear to markedly alter malaria incidence (rate ratio 1.07, 95% CI 0.80 to 1.43; 2 cRCTs, 15,717 child-years; moderate-certainty evidence), parasite prevalence (RR 1.11, 95% CI 0.86 to 1.44; 3 cRCTs, 10,820 participants; moderate-certainty evidence), or anaemia prevalence (RR 1.12, 95% CI 0.89 to 1.40; 1 cRCT, 4186 participants; low-certainty evidence). Data on EIR were limited so no conclusion was made (very low-certainty evidence).

Authors' conclusions

in communities using ITNs, the addition of IRS with 'non-pyrethroid-like' insecticides was associated with reduced malaria prevalence. Malaria incidence may also be reduced on average, but there was unexplained qualitative heterogeneity, and the effect may therefore not be observed in all settings.

When using 'pyrethroid-like' insecticides, there was no detectable additional benefit of IRS in communities using ITNs.

PLAIN LANGUAGE SUMMARY

Adding indoor residual spraying in communities using insecticide-treated nets for the prevention of malaria

What was the aim of this review?

Indoor residual spraying (IRS) is the regular application of chemical insecticides to household walls. The insecticide lasts for several months, killing mosquitoes that land on them. Insecticide-treated nets (ITNs) are bed nets treated with insecticides, preventing mosquitoes from biting people and reducing the mosquito population. Both interventions help to control malaria by reducing the number of people being bitten by mosquitoes infected with malaria. Implementing IRS in communities that are using ITNs may be better for malaria control than using ITNs alone simply because two interventions may be better than one; but also because it may improve malaria control where mosquitoes have become resistant to the pyrethroid insecticides used in ITNs. Pyrethroids were the only class of insecticides approved for use in ITNs until 2018, but growing resistance of mosquitoes to pyrethroids impairs their effectiveness. The addition of IRS could counteract this reduction in ITN effectiveness and may help to slow the emergence of pyrethroid resistance. We could expect that IRS insecticides that have a different way of working to pyrethroids ('non-pyrethroid-like') could restore effectiveness better than those that have the same way of working ('pyrethroid-like'). The aim of this review was to summarize the impact of pyrethroid-like or non-pyrethroid-like IRS on malaria, when implemented in communities that are using ITNs.

Key messages

The addition of IRS using a non-pyrethroid-like insecticide was associated with reduced malaria prevalence. Malaria incidence may also be reduced on average, but this effect was absent in two studies, and consequently there remains some uncertainty over whether the intervention will be effective in all settings.

When a pyrethroid-like insecticide was used for IRS, data were limited but there was no additional effect demonstrated.

What was studied in the review?

We searched for studies that evaluated the impact on malaria transmission when IRS, using a World Health Organization (WHO)-recommended dosage, was implemented in communities that were using either ready-treated ITN products or standard nets treated with insecticide at a WHO-recommended dose. We considered effects on both human health outcomes and on mosquito populations.

What were the main results of the review?

In total, we identified 10 studies matching our inclusion criteria, from which we made 12 comparisons. Seven studies (providing eight comparisons) used a non-pyrethroid-like IRS throughout the study. Each of these were conducted in areas where the vectors were described as resistant or highly resistant to pyrethroids. Two studies (providing two comparisons) used a pyrethroid-like IRS throughout. One further study used a pyrethroid-like IRS in the first study year and switched to a non-pyrethroid-like IRS in the subsequent years, therefore providing two different comparisons. All studies were conducted in sub-Saharan Africa.

Adding non-pyrethroid-like IRS in communities using ITNs appeared to improve malaria outcomes in most settings. Overall, the results from the eight included studies found lower malaria parasite prevalence, while there may be a reduction in malaria incidence and anaemia prevalence. We do not know if there is an impact on the number of infected bites received per person per year.

When adding pyrethroid-like IRS in communities using ITNs, the data from three studies indicate there is probably no effect on malaria incidence or parasite prevalence, and there may be little or no effect on the prevalence of anaemia. Data on the number of infected bites received per person per year were too limited to draw a conclusion.

How up to date is the review?

We searched for relevant studies up to 8 November 2021.

SUMMARY OF FINDINGS

Summary of findings 1. Non-pyrethroid-like indoor residual spraying (IRS) plus insecticide-treated nets (ITNs) versus ITNs alone for preventing malaria

Patient or population: people at risk of malaria

Setting: sub-Saharan Africa (Ethiopia, Mozambique, Tanzania, Sudan, Ghana, Uganda)

Intervention: combination of IRS + ITNs – using an insecticide for IRS that has a different target site to the pyrethroids used in ITNs

Comparison: ITNs alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments: the combination of IRS and ITNs, when the insecticide used for IRS has a different target site to the pyrethroids used in ITNs
	Risk with ITNs alone	Risk with IRS + ITNs				
Malaria incidence	357 cases per 1000 years at risk	307 cases per 1000 years at risk (218 to 439)	**Rate ratio 0.86** (0.61 to 1.23)	323,631 person-years at risk (4 comparisons, 4 cRCTs)	⊕⊕⊖⊖ **Low**[a,b]	May reduce malaria incidence compared to ITNs alone.
Malaria parasite prevalence	213 cases per 1000	119 cases per 1000 (90 to 158)	**RR 0.61** (0.42 to 0.88)	16,394 participants (5 comparisons, 4 cRCTs)	⊕⊕⊕⊕ **High**[c]	Reduces malaria parasite prevalence compared to ITNs alone.
EIR	—	—	**Not estimable** IRS was associated with a lower EIR in 2 of the 4 cRCTs	(5 comparisons, 4 cRCTs)	⊕⊖⊖⊖ **Very low**[d,e]	We did not know if there was an effect on the EIR compared to ITNs alone.
Anaemia prevalence	133 cases per 1000	94 cases per 1000 (50 to 174)	**RR 0.71** (0.38 to 1.31)	4288 participants (4 comparisons, 3 cRCTs)	⊕⊕⊖⊖ **Low**[a,f]	May have reduced anaemia prevalence compared to ITNs alone.

*__The risk in the intervention arm__ (and its 95% CI) is based on the assumed risk in the comparison arm and the **relative effect** of the intervention (and its 95% CI). The assumed risk of the comparison arm is calculated from the total number of events/total number of participants in the control arms of the trials contributing to the meta-analysis.

CI: confidence interval; **cRCT:** cluster randomized controlled trial; **EIR:** entomological inoculation rate; **IRS:** indoor residual spraying; **ITN:** insecticide-treated net; **RR:** risk ratio.

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]Downgraded one level for serious imprecision: the CIs were wide and included both a substantive decrease and no effect.
[b]Downgraded one level for serious inconsistency: four cRCTs contributed to the analysis. Two cRCTs did not demonstrate an effect of the intervention (Corbel 2012; Loha 2019), while two showed an effect. Two further quasi-experimental design studies showed an effect of the intervention, which was consistent with the overall meta-analysis. Consequently, there was considerable qualitative heterogeneity with an I^2 value of 87%. A subgroup analysis by ITN usage did not explain the heterogeneity. Although the cRCTs with no effect had low ITN usage in both arms and those with an effect had high ITN usage in both arms. this is counterintuitive, unless it reflects poor programme implementation for both ITNs and IRS.
[c]Not downgraded for inconsistency. In contrast to the four cRCTs included in the meta-analysis, one trial not included in the meta-analysis showed no effect of adding IRS (Corbel 2012). However, due to concerns over risk of bias in the data analysis leading to uncertainty over the size of the CIs calculated for this study, we cannot be certain that the absence of an effect in this trial is not a result of false precision.
[d]Downgraded one level for serious inconsistency: two trials reported a reduction in the outcome and two trials did not demonstrate an effect.
[e]Downgraded two levels for very serious imprecision. Where provided, the CIs for the mean EIR in the intervention arms were very wide, including values that would represent both large increases and reductions from the mean EIR in the control arms. The trial showing the largest reduction in EIR did not report CIs for this outcome and it is, therefore, difficult to assess the precision (Protopopoff 2018).
[f]Downgraded one level for serious inconsistency: there was moderate heterogeneity with an I^2 value of 49%. One study reported a substantial reduction in anaemia and another reported a moderate reduction. Two comparisons in the subgroup showed no effect by adding IRS, though it should be noted that one of these comparisons assessed the addition of IRS to pyrethroid-PBO nets (Protopopoff 2018).

Summary of findings 2. Pyrethroid-like indoor residual spraying (IRS) + insecticide-treated nets (ITNs) versus ITNs alone for preventing malaria

Patient or population: people at risk of malaria

Setting: sub-Saharan Africa (The Gambia, Sudan, Eritrea)

Intervention: combination of IRS + ITNs – using an insecticide for IRS that has the same target site as the pyrethroids used in ITNs

Comparison: ITNs alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments: the combination of IRS and ITNs, when the insecticide used for IRS has the same target site as the pyrethroids used in ITNs
	Risk with ITNs alone	Risk with IRS + ITNs				
Malaria incidence	215 cases per 1000 child-years	230 cases per 1000 child-years (172 to 307)	**Rate ratio 1.07** (0.80 to 1.43)	15,717 child-years (2 comparisons, 2 cRCTs)	⊕⊕⊕⊖ **Moderate**[a]	Probably had little or no effect on malaria incidence compared to ITNs alone.

Malaria parasite prevalence	13.2 cases per 100	14.7 cases per 100 (11.4 to 19.0)	**RR 1.11** (0.86 to 1.44)	10,820 participants (4 comparisons, 3 cRCTs)	⊕⊕⊕⊖ **Moderate**[a]	Probably had little or no effect on malaria parasite prevalence compared to ITNs alone.
EIR	—	—	Mean EIR was lower with IRS + ITNs than ITNs alone	(2 comparisons, 1 cRCT)	⊕⊖⊖⊖ **Very low**[b,c]	We do not know if there was an effect on the EIR compared to ITNs alone.
Anaemia prevalence (haemoglobin < 8 g/dL)	42.6 cases per 100	47.7 cases per 100 (37.9 to 59.6)	**RR 1.12** (0.89 to 1.40)	4186 participants (2 comparisons, 1 cRCTs)	⊕⊕⊖⊖ **Low**[a,b]	May have had little or no effect on anaemia prevalence compared to ITNs alone.

*__The risk in the intervention arm__ (and its 95% CI) is based on the assumed risk in the comparison arm and the **relative effect** of the intervention (and its 95% CI). The assumed risk of the comparison arm is calculated from the total number of events/total number of participants in the control arms of the trials contributing to the meta-analysis.

CI: confidence interval; **cRCT:** cluster randomized controlled trial; **IRS:** indoor residual spraying; **ITN:** insecticide-treated net; **RR:** risk ratio.

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]Downgraded one level for serious imprecision: the CIs were wide and included both an increase and decrease in the outcome.
[b]Downgraded one level for serious indirectness: the evidence was provided from one trial only and it was not certain that the reported effect would be seen in other malaria transmission settings.
[c]Downgraded two levels for very serious imprecision: the CIs for the mean EIR in the intervention arms were very wide, including values that would represent both large increases and reductions from the mean EIR in the control arms.

BACKGROUND

Description of the condition

Between 2000 and 2015, malaria deaths halved globally. In this time, malaria control interventions were estimated to have averted 663 million cases of malaria, with much of the progress attributed to vector control (Bhatt 2015). Despite this decline, the disease is still a leading cause of mortality, responsible for 409,000 deaths worldwide in 2019 (WHO 2020).

Description of the intervention

Vector control depends largely on insecticides, primarily delivered as indoor residual spraying (IRS) or insecticide-treated nets (ITNs). IRS is the regular spraying of insecticides to the indoor walls of houses. The insecticide lasts for at least four months, killing mosquitoes that land on it. ITNs are bed nets treated with insecticides, preventing mosquitoes from biting people and reducing the mosquito population. ITNs include long-lasting insecticidal nets (LLINs), where the insecticide lasts for up to three years, and conventionally treated nets, where the insecticide is active for up to 12 months. Up until 2018, only nets treated with pyrethroids were recommended by the World Health Organization (WHO) (Zaim 2000). Since 2018, piperonyl butoxide (PBO) added to pyrethroid nets was also recommended by the WHO, making them more effective at killing mosquitoes in areas where the mosquito populations are highly resistant to pyrethroids (Gleave 2018). Insecticides used for IRS are less restricted, as people living in the households are considered less likely to come into contact with the treated walls than with the fabric of a bed net.

Pyrethroids target the mosquito voltage-gated sodium ion channels. If mosquito resistance to pyrethroids is leading to reduced effectiveness of ITNs, IRS using insecticides with different target sites ('non-pyrethroid-like' insecticides) may be less affected by the pyrethroid resistance and more likely to have an impact on malaria transmission. In contrast, IRS using insecticides that also target the voltage-gated sodium ion channels ('pyrethroid-like' insecticides) may be less likely to have an impact.

How the intervention might work

IRS with dichloro-diphenyl-trichlorethane (DDT) was the main intervention of the malaria eradication programmes in the mid-20th century (Pluess 2010). When malaria was eliminated from many parts of South America, Europe, and Asia, IRS was an integral part of the elimination strategies (Pluess 2010). However, many countries today choose to adopt ITNs rather than IRS, as they are logistically easier to implement than IRS and more acceptable to communities.

Theoretically, the simultaneous use of IRS and ITNs is better for malaria control than using ITNs alone for two main reasons. First, we might expect an incremental effect of using two vector control interventions over one, particularly when the major vector species that are targeted largely feed and largely rest indoors (endophagic and endophilic vectors). As with many vector control interventions, the reality is not simple and the success of the intervention will depend on both human and vector behaviour (Killeen 2006). Mosquito exophily can reduce the effectiveness of IRS and ITNs, as mosquitoes that rest outdoors more will have less contact with an indoor treated wall or net (Kitau 2012). Earlier biting times of *Anopheles* spp have also been observed, which can increase the likelihood of a mosquito encountering a human to bite and reduce the impact of ITNs (Ojuka 2015).

Second, implementing IRS in communities currently using ITNs may be beneficial for the management of mosquito resistance to insecticides. Malaria control programmes may additionally implement IRS as a reactive measure in response to high pyrethroid resistance in *Anopheles* mosquitoes. The addition of IRS could mitigate for this reduction in ITN effectiveness. In particular, non-pyrethroid-like IRS may be expected to show additional impact in instances where mosquitoes are resistant to pyrethroids on ITNs but susceptible to non-pyrethroids that can be delivered via IRS. Policy-makers could also introduce a combination of the two interventions proactively, administering a non-pyrethroid-like IRS alongside ITNs as part of an insecticide resistance management (IRM) strategy to delay the emergence of pyrethroid resistance (WHO 2012).

Why it is important to do this review

The combination of IRS and ITNs can be logistically complicated to deliver. ITNs are advantageous because they can last for three to five years, and because net distribution campaigns can be conducted at a village central point or community health centre. In contrast, the current set of insecticides used for IRS will remain active for one year at best, and an effective spray campaign in a setting with perennial malaria transmission will, therefore, require several sprays per year (WHO 2015a). IRS is also logistically more demanding, requiring a visit to every individual household. IRS programmes typically take a substantially higher amount of financial commitment than an ITN distribution campaign, in part due to the sheer quantity of insecticide required at programmatic scales (Goodman 2001). Finally, IRS has experienced more problems with the acceptability of the intervention and its delivery than ITNs (Kleinschmidt 2009).

The impact on malaria transmission of combining IRS with ITNs is not fully understood. A previous version of this review found that, in communities using ITNs, the addition of IRS using a pyrethroid-like insecticide probably had no effect on malaria incidence or prevalence. The effect of adding IRS with a non-pyrethroid-like insecticide was uncertain, with inconsistent results reported across a limited number of studies (Choi 2019). The current global guidelines for malaria vector control recommend against implementing IRS as a second intervention in areas that have suboptimal coverage of ITNs, and vice versa, stating that priority should instead be given to ensuring optimal coverage of the first intervention. In areas that have achieved optimal coverage of a first intervention, programmes may consider implementing a second intervention for the purposes of IRM, though the insecticides used for IRS and ITNs must not be of the same class (WHO 2019).

A greater understanding of the impact of IRS in combination with ITNs, particularly when using insecticides of different classes, will help to determine whether the additional logistical complexity is worthwhile. Since the publication of the last updates, several new studies have been published that add to the available literature.

OBJECTIVES

To summarize the effect on malaria of additionally implementing IRS, using non-pyrethroid-like or pyrethroid-like insecticides, in communities currently using ITNs.

METHODS

Criteria for considering studies for this review

Types of studies

- Randomized controlled trials (RCTs) with: the unit of randomization being a cluster and at least two clusters per arm (cRCTs). As the two interventions were distributed at a community level, we did not expect to find trials with individual randomization.
- Controlled before-after studies (CBAs) with: a contemporaneous control arm and at least two sites per arm.
- Interrupted time series designs (ITS) with: a clearly defined point in time when the intervention occurred and at least three data points before and three after the intervention.

Types of participants

All people living in a rural or urban malarious area where ITNs were in use. We included participants living in all levels of endemicity, including both stable and unstable transmission.

Types of interventions

IRS using the WHO-recommended dosage (see Table 1; WHO 2015a). We individually evaluated the effects of IRS using:

- 'non-pyrethroid-like insecticides': those with alternative targets such as acetylcholinesterase, in contrast to ITNs;
- 'pyrethroid-like insecticides': those that target the voltage-gated sodium ion channels, similarly to ITNs.

ITNs interventions were required to be the same in both intervention and control arms. Suitable ITNs included LLINs and pyrethroid-PBO nets, with either a full or preliminary recommendation by the WHO (Table 2), or conventionally treated nets, treated with insecticide at the WHO-recommended dosage (Table 3). Only studies with at least 50% ITN ownership (defined as the proportion of households owning one or more ITN) in both study arms were considered suitable for inclusion.

Any other malaria control measures were required to be the same in both intervention and control arms.

Types of outcome measures

Primary outcomes

Studies eligible for inclusion must have reported at least one of the following.

- Malaria incidence: measured as a count per person unit time of 1. infections or 2. new infections, following treatment to avoid measuring pre-existing infections. Infection was defined as any symptom, including fever, with confirmed parasitaemia (by blood smear microscopy or rapid diagnostic test (RDT)).
- Malaria parasite prevalence: the proportion of surveyed people with confirmed parasitaemia.

Secondary outcomes

Entomological

- Entomological inoculation rate (EIR): the estimated number of bites by infectious mosquitoes per person per unit of time. This was measured using the human biting rate (the number of mosquitoes biting a person over a stated period measured directly using human baits or indirectly using light traps, knock-down catches, baited huts, or other methods of biting rate determination) multiplied by the sporozoite rate.
- Sporozoite rate: the fraction of vector mosquitoes present and biting that were considered infectious, measured by a technique previously shown to be appropriate for the vector (microscopy, immunoassays, polymerase chain reaction-based assays or other methods).
- Adult mosquito density: measured by a technique previously shown to be appropriate for the vector (human baits, light traps, knock-down catches, baited huts, or other methods).

Epidemiological

- Malaria-related deaths.
- Anaemia prevalence defined as per WHO cut-offs (WHO 2011).
- Hospital admissions for malaria.
- Number of people with severe malaria: using site-specific definitions, provided they included 1. and either 2. or 3.: 1. demonstration of parasitaemia by blood smear; 2. symptoms of cerebral malaria including coma, prostration, or multiple seizures; 3. severe, life-threatening anaemia (WHO 2015b).
- Number of people with uncomplicated clinical malaria episodes: we will use site-specific definitions, provided they included: 1. demonstration of malaria parasites by blood smear or an RDT, or both; and 2. clinical symptoms including fever detected passively or actively.

Mosquito insecticide resistance

- Level of insecticide resistance, confirmed by WHO cylinder assays/Centers for Disease Control and Prevention (CDC) bottle bioassays or molecular techniques. This included resistance to either the class of insecticide used for IRS (i.e. as an unwanted outcome of studies due to increased coverage of insecticidal interventions) or to pyrethroid insecticides (to monitor whether the addition of IRS prevented or reduced resistance to ITNs).

Search methods for identification of studies

We attempted to identify all relevant studies regardless of language or publication status (published, unpublished, in press, and in progress).

Electronic searches

We searched the following databases from 1 January 2000 to 8 November 2021, on the basis that ITN programmes did not begin to be implemented as policy before the year 2000. We used the search terms and strategy described in Appendix 1: Cochrane Infectious Diseases Group Specialized Register; Cochrane Central Register of Controlled Trials(CENTRAL) Issue 3, April 2019, published in the Cochrane Library; MEDLINE (PubMed); Embase (Ovid); and LILACS (Bireme). We also checked the WHO International Clinical Trials Registry Platform (WHO ICTRP; www.who.int/ictrp/en/) and ClinicalTrials.gov (clinicaltrials.gov/ct2/home) for ongoing trials on 8 November 2021, using the terms: indoor residual spraying; IRS; insecticide-treated nets; bednets; ITNs; LLIN.

Searching other resources

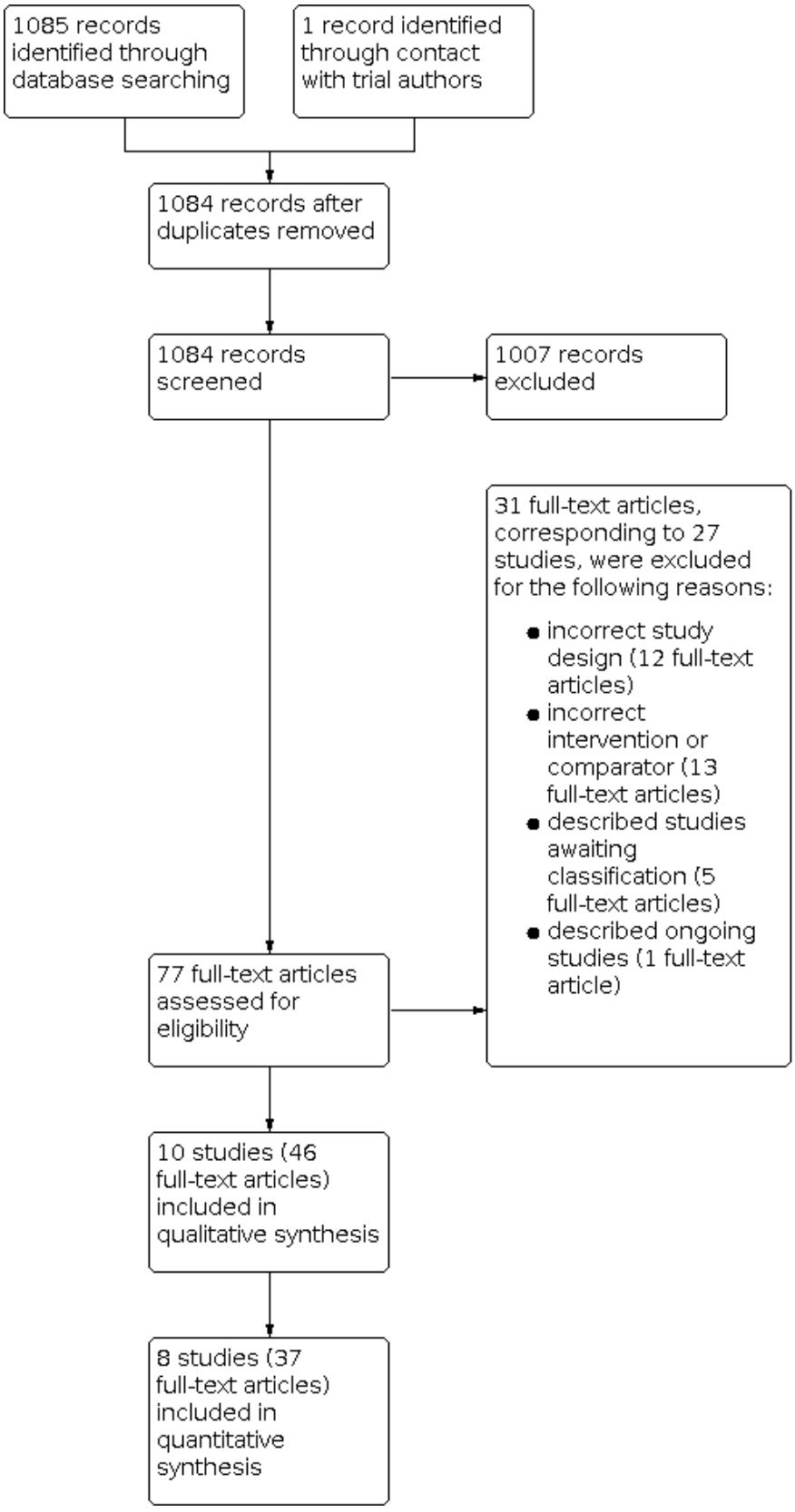
We contacted researchers working in the field for unpublished data. We also checked the reference lists of all studies identified by the above methods.

Data collection and analysis

Selection of studies

At least two review authors independently assessed the titles and abstracts of each identified study, with all three review authors contributing to this process. Similarly, a minimum of two of the three review authors accessed and assessed the full-text copies of each potentially relevant study for inclusion using an eligibility form based on the inclusion criteria. Any disagreements between the two review authors were resolved by discussion and consensus, with arbitration by the third review author when necessary. We ensured that multiple publications of the same study were included once. We listed excluded studies, together with their reasons for exclusion, in the Characteristics of excluded studies table. We illustrated the study selection process in a PRISMA diagram (Figure 1).

Figure 1. Study flow diagram.



Data extraction and management

Two of the three authors independently extracted information from the studies using prepiloted, electronic data extraction forms. In case of differences in extracted data, the two review authors discussed these differences to reach consensus. If unresolved, they consulted the third review author. In case of missing data, we contacted the original study author(s) for clarification.

We extracted data on the following.

- Study design: type of study; method of participant selection; adjustment for clustering (for cRCTs); sample size; method of blinding of participants and personnel.
- Participants: study settings and population characteristics; recruitment rates; withdrawal and loss to follow-up.
- Intervention: description of IRS (active ingredient, dose, formulation, method, frequency and timing of application, coverage – defined as proportion of eligible structures sprayed, buffer zone between clusters); description of ITNs (ITN type, timing of distribution, ITN ownership – defined as proportion of households owning at least one ITN – or other measurement of ITN coverage; ITN use – defined as proportion of individuals using an ITN the previous night – or other measurement of ITN use); description of cointerventions (type, frequency of application, compliance of cointervention).
- Outcomes: definition of outcome; diagnostic method or surveillance method; passive or active case detection; duration of follow-up; time points at which outcomes were assessed; number of events; number of participants or unit time; statistical power; unit of analysis; incomplete outcomes/missing data.
- Other:
  - primary and secondary vector(s) species; vector(s) behaviour (nature, stability, adult habitat, peak biting times, exophilic/endophilic, exophagic/endophagic, anthropophilic/zoophilic); method of mosquito collection(s); phenotypic insecticide resistance (based on WHO definitions if supplementary WHO cylinder assays or CDC bottle bioassays, or both, were performed while the study was running); genotypic insecticide resistance profile (either performed during the study or if the study referenced data from previous studies done on the same local vector population within the previous five years);
  - malaria endemicity; eco-epidemiological setting; human population proximity to mosquito aquatic habitats, human population density per area; *Plasmodium* spp.

For dichotomous outcomes, we extracted the number of participants experiencing each outcome and the number of participants in each treatment arm. For count/rate data outcomes, we extracted the number of outcomes in the treatment and control arms, and the total person time at risk in each arm or the rate ratio, and a measure of variance (e.g. standard error). For continuous outcomes, we extracted the mean and a measure of variance (standard deviation).

For cRCTs, we recorded the number of clusters randomized; number of clusters analyzed; measure of effect (such as risk ratio (RR), odds ratio, or mean difference (MD)) with 95% confidence intervals (CI) or standard deviations; number of participants; and the intracluster correlation coefficient (ICC) value. Where studies reported cluster-adjusted odds ratios, we converted these to RRs following the methodology stated in Section 12.5.4.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a).

For quasi-experimental design studies, we extracted adjusted measures of intervention effects that attempted to control for confounding.

Assessment of risk of bias in included studies

Two of the three review authors independently assessed the risk of bias for each included cRCT using the Cochrane risk of bias tool and the five additional criteria listed in Section 16.3.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* that relate specifically to cRCTs (Higgins 2011a; Higgins 2011b). We assessed the risk of bias for CBA using Cochrane EPOC's 'Risk of bias criteria for studies with a separate control group' and for ITS studies we used 'Risk of bias criteria for interrupted time series studies' (EPOC 2017). We resolved any discrepancies through discussion or by consulting a third review author if necessary. We classified judgements of risk of bias as at low, high, or unclear risk of bias, and we used summary graphs (risk of bias summary and risk of bias graph) to display results.

Due to the nature of the IRS application, blinding of participants and study personnel was not possible. When assessing the risk of performance bias, we considered that the primary outcomes of malaria incidence and malaria parasite prevalence were unlikely to be affected by participant knowledge of the intervention. Therefore, we did not associate the lack of participant blinding with a high risk of performance bias. When assessing the risk of detection bias, we considered that measurements of incidence that depended on self-reporting of fever may have been influenced by the participants' knowledge of the intervention. However, to meet the inclusion criteria for this review, such cases required confirmation of parasitaemia by blood smear microscopy or RDT, and the results of these objective tests were considered unlikely to be influenced by knowledge of the intervention arm. Therefore, where studies measured incidence using this method, we considered the lack of blinding to introduce an unclear risk of bias; this is consistent with the methods used by Pryce 2018.

Measures of treatment effect

We compared intervention and control data using RRs and for count/rate data, we used rate ratios. We used adjusted measures of effect to summarize treatment effect from quasi-experimental design studies. We presented all results with their associated 95% CIs.

Unit of analysis issues

For cRCTs, or cluster quasi-experimental design studies, we extracted adjusted measures of effect where possible. 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 2011a), which was determined by the ICC. If the study did not report the ICC value, we estimated the ICC value using a range of 0.01, 0.05, and 0.1. When we estimated the ICC, we performed sensitivity analyses to investigate the robustness of our analyses.

If we identified studies for inclusion that had multiple intervention arms, we included data from these studies by either combining

treatment arms, or by splitting the control arm so that we only included these participants in the meta-analysis once.

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 planned to perform analyses on an intention-to-treat basis. We included all participants randomized to each arm in the analyses and analyzed participants in the arm 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 statistic. We regarded heterogeneity as moderate if the I^2 statistic was between 30% and 60%; substantial if it was between 59% and 90%; and considerable if it was between 75% and 100% (Deeks 2011). We regarded a Chi^2 test statistic with a $P \leq 0.10$ indicative of statistically significant heterogeneity. We explored clinical and methodological heterogeneity through consideration of the study populations, methods, and interventions, and by visualization of study results.

Assessment of reporting biases

If there were 10 or more studies included in each meta-analysis, we intended to investigate reporting biases (such as publication bias) using funnel plots. We would have assessed funnel plot asymmetry visually, and used formal tests for funnel plot asymmetry (Harbord 2006). If we detected asymmetry in any of these tests or by a visual assessment, we would have explored the reasons for asymmetry. However, we did not identify 10 or more studies contributing to any meta-analysis, and, therefore, could not investigate reporting bias using a funnel plot. Instead, we compared the outcomes reported against the study protocols.

Data synthesis

We analyzed data using Review Manager 5 (Review Manager 2020). We used fixed-effect meta-analysis to combine data if heterogeneity was absent. For a meta-analysis of reported effect sizes, we used a generic inverse variance model. Where raw data were used for a meta-analysis of RRs, we used a Mantel-Haenszel model. For meta-analysis of RRs and odds ratios, if considerable heterogeneity was present, we combined data using random-effects meta-analysis and reported a mean treatment effect. We decided whether to use fixed-effect or random-effects models based on the consideration of clinical and methodological heterogeneity between studies, as described previously.

Subgroup analysis and investigation of heterogeneity

To explore reasons for substantial heterogeneity, we performed the following subgroup analysis.

- Use of ITNs, defined as the proportion of individuals who slept under an ITN the previous night:
  - high (80% or more);
  - moderate (50% to 79%);
  - low (less than 50%);
  - note: studies that did not report this outcome, but instead reported an alternative measurement of ITN use (e. proportion of households in which one or more individuals slept under an ITN the previous night) were not included in this analysis.
- Coverage of IRS, defined as the percentage of eligible structures in the intervention region that were sprayed:
  - high (80% or more);
  - moderate (50% to 79%);
  - low (less than 50%.

We assessed differences between the subgroups using the Chi^2 test, with a P value less than 0.1 indicating statistically significant differences between subgroups.

Sensitivity analysis

We performed sensitivity analyses on the primary outcomes to see the effect of exclusion of studies at high risk of bias. Where the exclusion of studies at high risk of bias led to significant changes in the pooled analysis, we excluded such studies from the meta-analysis.

Summary of findings and assessment of the certainty of the evidence

We assessed the certainty of the evidence using the GRADE approach (Guyatt 2011). We rated each important outcome as described by Balshem 2011.

- 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.

RCTs started as high-certainty evidence and quasi-experimental design studies started as low-certainty evidence. The certainty of the evidence was downgraded if there were valid reasons within the following five categories: risk of bias, imprecision, inconsistency, indirectness, and publication bias. The evidence could also be upgraded if there was a large effect, a dose–response effect, and if all plausible residual confounding would reduce a demonstrated effect or would suggest a spurious effect if there was no effect observed (Balshem 2011). We summarized our findings in Summary of findings 1 and Summary of findings 2.

RESULTS

Description of studies

We provided descriptions of the included and excluded studies in the Characteristics of included studies and Characteristics of excluded studies tables. Studies awaiting classification were described in the Characteristics of studies awaiting classification table, and ongoing studies in the Characteristics of ongoing studies table.

Results of the search

We identified 1085 reports through the electronic search and one additional report through contact with study authors. We removed two duplicates and screened the remaining 1084 abstracts against the review's inclusion criteria. Of these, we identified 77 unique reports for full-text screening (Figure 1). We included 10 studies (46 articles) and excluded 21 studies (31 articles).

Included studies

Overall, 46 reports corresponding to 10 studies met the inclusion criteria, from which 12 comparisons were drawn. Seven studies (providing eight comparisons) used a non-pyrethroid-like IRS throughout the study (Chaccour 2021; Corbel 2012; Gogue 2020; Namuganga 2021; Loha 2019; Protopopoff 2018; West 2014). Two studies (providing two comparisons) used a pyrethroid-like IRS throughout (Keating 2011; Pinder 2015). One study used a pyrethroid-like insecticide in the first study year, but replaced it with a non-pyrethroid-like insecticide for the two subsequent years, and, therefore, provided two different comparisons (Kafy 2017). As the mean residual efficacy of the deltamethrin insecticide used in the first year is less than six months, it is not expected that any impact from the first year's intervention would carry over into the subsequent years' comparison. Consequently, overall, eight studies contributed to Comparison 1: IRS using non-pyrethroid-like insecticides, while three studies contributed to Comparison 2: IRS using pyrethroid-like insecticides.

Comparison 1: indoor residual spraying using non-pyrethroid-like insecticides

The eight studies evaluating the effect of non-pyrethroid-like IRS comprised six cRCTs and two quasi-experimental design studies. Four of the six cRCTs evaluated the effect of adding IRS to ITNs using a two-armed study design (Chaccour 2021; Kafy 2017; Loha 2019; West 2014). The remaining two cRCTs had four arms. Corbel 2012 compared universal coverage of ITNs (defined as one ITN per sleeping unit); universal coverage of ITNs plus carbamate-treated plastic sheeting; targeted ITNs (defined as one ITN per sleeping unit of children younger than 6 years or pregnant women); and targeted ITNs plus IRS. The latter two arms provide the comparison for this review. Protopopoff 2018 used a 2 × 2 factorial design which compared standard LLINs; standard LLINs plus IRS; pyrethroid-PBO nets; and pyrethroid-PBO nets plus IRS. The former and latter two arms each provide a comparison for this review. The two quasi-experimental design studies included one CBA (Gogue 2020) and one ITS design (Namuganga 2021).

Each of the eight studies were conducted in sub-Saharan Africa. Of the six cRCTs, one was conducted in Ethiopia (Loha 2019); one in south-east Sudan (Kafy 2017), one in Mozambique (Chaccour 2021), one in Benin (Corbel 2012), and two in north-west Tanzania (Protopopoff 2018; West 2014). The two quasi-experimental design studies were conducted in Ghana (Gogue 2020) and Uganda (Namuganga 2021). All eight studies were conducted in areas where the primary vectors were described as resistant or highly resistant to pyrethroid insecticides. The study sites in Ethiopia and south-east Sudan were described as experiencing seasonal transmission, while those in Benin, Ghana, Uganda, Mozambique, and north-west Tanzania were described as perennial transmission areas. None of the studies were conducted in exclusively epidemic areas.

Interventions

Coverage

Three studies described IRS application coverage as between 80% and 90% of households in the study area (Chaccour 2021; Kafy 2017; West 2014), and the remaining five studies as above 90% (Corbel 2012; Gogue 2020; Loha 2019; Namuganga 2021; Protopopoff 2018).

Insecticide

Three studies implemented IRS using a wettable powder (WP) formulation of the carbamate bendiocarb, at a dose of 400 mg/m^2 (Corbel 2012; Namuganga 2021; West 2014). One study switched from a pyrethroid-like IRS to bendiocarb in the second year of the study (Kafy 2017). One study stopped using bendiocarb in the third year of the study and began implementing IRS with another non-pyrethroid-like insecticide: Actellic 300CS (a commercial formulation of pirimiphos-methyl) (Namuganga 2021). Three studies used Actellic 300CS throughout, at a dose of 1 g/m^2 (Chaccour 2021; Gogue 2020; Protopopoff 2018). The remaining study used Propoxur WP at a dose of 2 g/m^2 (Loha 2019).

Frequency

The frequency of spraying varied depending on the eco-epidemiological conditions of each location and the type of insecticide used. Three studies conducted two rounds per year, approximately four months apart, preceding each of two annual transmission peaks (Kafy 2017; Namuganga 2021; West 2014), though Namuganga 2021 implemented Actellic 300CS IRS annually for the final two years of the study. Two studies repeated the IRS cycle annually (Chaccour 2021; Loha 2019), and two studies conducted only one spraying round (Gogue 2020; Protopopoff 2018). Full characteristics of the interventions are summarized in Table 4.

Insecticide-treated nets in intervention and control arms

ITN ownership, defined as the proportion of households owning at least one ITN, was high (80% or higher) in six studies (Chaccour 2021; Gogue 2020; Kafy 2017; Loha 2019; Namuganga 2021; Protopopoff 2018). The remaining two studies reported alternative measures of coverage. West 2014 reported the proportion of households with at least one ITN per sleeping space (51.6% to 52.8%). Corbel 2012 reported the proportion of sleeping units protected by an ITN (38% to 45%). Notably, this study aimed to evaluate the use of targeted ITNs (covering pregnant women and children under six years old only) and, therefore, did not aim for full coverage of the population. Both West 2014 and Corbel 2012 were considered to have met the inclusion criteria of 50% of households owning at least one ITN, but as this specific proportion was not reported, these studies were not given a high, moderate, or low ownership rating. In each of the eight included studies, ITN distribution was equal between the intervention and control arms.

ITN use (defined as the proportion of individuals using an ITN the previous night) was high (80% or higher) in three studies (Chaccour 2021; Kafy 2017; Namuganga 2021), moderate (50% to 79%) in two studies (Gogue 2020; Protopopoff 2018), and low (less than 50%) in two studies (Corbel 2012; West 2014). Loha 2019 did not report the proportion of individuals using an ITN the previous night, and was, therefore, not given a high, moderate, or low rating for ITN use. Instead, Loha 2019 reported the proportion of households in which one or more individuals used an ITN the

previous night. This proportion declined during the study, from 47% to 49% in the first six months of the study to less than 10% after one year. Specific measurements of ITN ownership and use for each study are summarized in Table 5.

In three studies, the ITN distributed was the deltamethrin-based PermaNet 2.0 (Corbel 2012; Kafy 2017; Loha 2019), one study distributed alphacypermethrin-treated nets (Chaccour 2021), while two studies involved distribution of the permethrin-based Olyset Net (Protopopoff 2018; West 2014). In the two arms that evaluated the efficacy of pyrethroid-PBO nets, Protopopoff 2018 used Olyset Plus instead of Olyset Net. The two quasi-experimental design studies did not provide details of the ITN distributed but stated that a mass distribution campaign had recently taken place (Gogue 2020; Namuganga 2021).

Cointerventions

The studies did not report on any cointerventions.

Outcomes

Epidemiological

Two cRCTs and one quasi-experimental design study reported clinical malaria outcomes in people of all ages (Chaccour 2021; Gogue 2020; Loha 2019), while four cRCTs and one quasi-experimental design study measured these outcomes in children only; one in children under six years of age (Corbel 2012); one in children aged six months to 10 years (Namuganga 2021); one in children aged one to 10 years (Kafy 2017) and two in children aged between six months and 14 years (Protopopoff 2018; West 2014). Of the two primary outcomes, four cRCTs (Chaccour 2021; Corbel 2012; Kafy 2017; Loha 2019) and two quasi-experimental design studies (Gogue 2020; Namuganga 2021) measured malaria incidence. Five cRCTs measured malaria parasite prevalence (Chaccour 2021; Corbel 2012; Kafy 2017; Protopopoff 2018; West 2014). Three studies also reported the prevalence of childhood anaemia (Loha 2019; Protopopoff 2018; West 2014). Protopopoff 2018 limited their analysis of anaemia to children aged six months to four years. We extracted the nine-month postintervention cross-sectional survey results only, as IRS was not conducted beyond this time point, which acted as their main endpoint for assessing the efficacy of IRS (Protopopoff 2018).

Entomological

Four cRCTs reported the estimated EIR (Chaccour 2021; Corbel 2012; Protopopoff 2018; West 2014), and two cRCTs reported the sporozoite rate (Protopopoff 2018; West 2014). Five cRCTs and one quasi-experimental design study reported a measure of the adult mosquito density (Chaccour 2021; Corbel 2012; Loha 2019; Namuganga 2021; Protopopoff 2018; West 2014).

Mosquito insecticide resistance

One study additionally reported the prevalence in malaria vectors of alleles associated with resistance to pyrethroids (1014F kdr) and carbamates (G119S ace1) (Corbel 2012). One study reported the level of phenotypic resistance to pyrethroids (Kafy 2017).

Comparison 2: insecticide-treated nets using pyrethroid-like insecticides

The three cRCTs evaluating pyrethroid-like IRS were conducted in sub-Saharan Africa; in the west lowlands of Eritrea (Keating 2011), the upper river region of The Gambia (Pinder 2015), and in south-east Sudan (Kafy 2017). Each study area was described as seasonal transmission areas.

Interventions

Coverage

IRS application coverage was described as consistently above 80% (Kafy 2017), 84.8% (Keating 2011), and 83% to 86% (Pinder 2015).

Insecticide

Two studies used a WP formulation of DDT, at a dose of 1 g/m^2 to 2 g/m^2 (Keating 2011; Pinder 2015). One study used the pyrethroid deltamethrin at a dose of 25mg/m^2 in the first study year (Kafy 2017).

Frequency

The frequency of spraying varied depending on the eco-epidemiological conditions of each location. One study conducted IRS once per year to coincide with the start of the transmission season (Pinder 2015). One study conducted two rounds, four months apart, preceding each of two annual transmission peaks (Kafy 2017). One study conducted only one spraying round (Keating 2011). Full characteristics of the interventions have been summarized in Table 4.

Insecticide-treated nets in intervention and control arms

ITN ownership, defined as the proportion of households owning at least one ITN, was reported as high (80% or higher) in two studies (Kafy 2017; Pinder 2015). The remaining study, Keating 2011, reported an alternative measure of ITN coverage; the proportion of people living in households with at least one ITN (72% to 75.8%). Consequently, although this study was considered to have met the inclusion criteria of 50% household ITN ownership, it was not given a high, moderate, or low ITN ownership rating. ITN distribution was equal between the intervention and control arms in all three studies.

ITN use (defined as the proportion of individuals using an ITN the previous night) was high (80% or higher) in two studies (Kafy 2017; Pinder 2015) and moderate (50 to 79%) in one study (Keating 2011).

Specific measurements of ITN ownership and use for each study are summarized in Table 5.

In one study, the ITN distributed was the deltamethrin-based PermaNet 2.0 (Kafy 2017), while one study involved distribution of the permethrin-based Olyset Net (Pinder 2015). One study did not distribute ITNs as the region already had high ITN ownership; any LLIN, or ITN that had been treated at least once in the last 11 months, was considered acceptable when measuring net ownership in this study (Keating 2011).

Cointerventions

One study listed larval habitat management and continued case management as cointerventions that were conducted in both intervention and control arms during the study period (Keating 2011). The remaining studies did not report on any cointerventions.

Outcomes

Epidemiological

Two studies measured clinical outcomes in children only; one in children aged one to 10 years of age (Kafy 2017), and one in children aged between six months and 14 years (Pinder 2015). The third study measured outcomes in participants of all ages (Keating 2011). Of the two primary outcomes, two studies measured malaria incidence (Kafy 2017; Pinder 2015), and all three studies measured malaria parasite prevalence. One study also reported the prevalence of childhood anaemia (Pinder 2015). For malaria parasite prevalence and anaemia prevalence, Pinder 2015 reported separately adjusted effect estimates for both years of the study, 2010 and 2011, so we included both estimates in the analysis separately.

Entomological

One study reported the estimated EIR, sporozoite rate, and adult mosquito density measured as the number of adult *Anopheles gambiae s.l.* collected per trap per night (Pinder 2015).

Mosquito insecticide resistance

One study measured the prevalence of alleles associated with pyrethroid resistance only (Kafy 2017).

Excluded studies

We excluded 25 full-text articles, corresponding to 21 unique studies, for the following reasons:

- study design did not meet the inclusion criteria (12 full-text articles, 9 unique studies);
- interventions in the experimental or comparator arms did not meet the inclusion criteria (13 full-text articles, 12 unique studies).

Full details are provided in the Characteristics of excluded studies tables.

Studies awaiting classification

Five articles describing five studies are currently reported in the Characteristics of studies awaiting classification table. One described a study of stepped wedge design, for which the results are not presented in a form that can be used in this analysis; we have requested additional data from the study authors (Hamainza 2016). One article described a small entomological cross-sectional survey but referred to an over-arching RCT that may be measuring epidemiological outcomes; we have contacted the authors for further information regarding this RCT to determine whether it would meet the reviews' inclusion criteria (Soma 2021). The remaining three articles were conference abstracts for which there was insufficient information to determine whether the inclusion criteria are met; we have requested additional data from the study authors (Omondi 2019; Turnbull 2018; Zogo 2019).

Ongoing studies

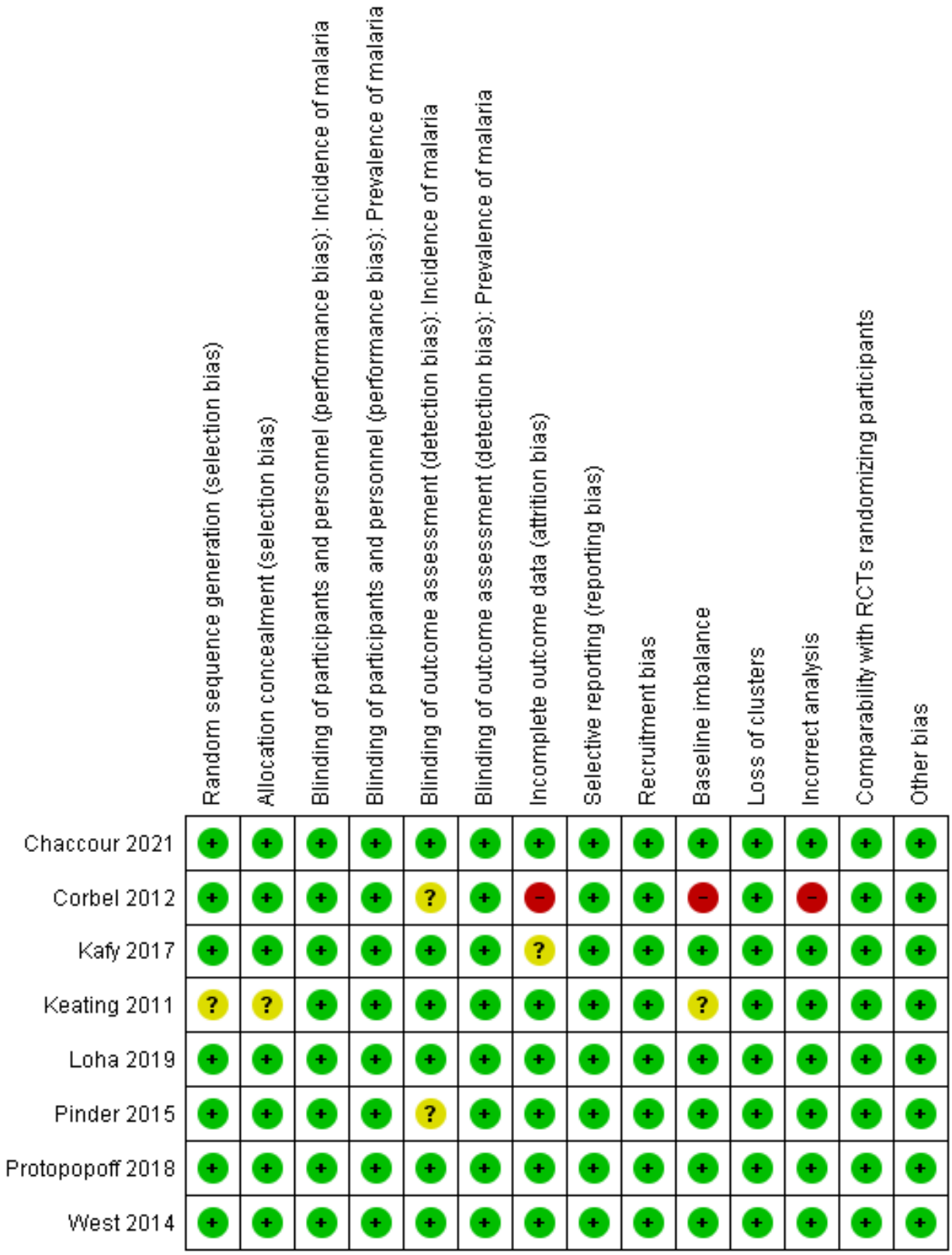
We identified one study protocol published in 2020 for a randomized trial that is scheduled to take more than three years to complete (Zhou 2020). Further information regarding this ongoing study is provided in the Characteristics of ongoing studies table.

Risk of bias in included studies

Risk of bias in randomized controlled trials

Overall, the included cRCTs were well designed, with only one study causing concern over risk of bias (Figure 2). Details of the assessment are included in the risk of bias table of the Characteristics of included studies table.

Figure 2. Risk of bias (randomized controlled trials): summary of review authors' judgements about each risk of bias item



Allocation

We assessed seven cRCTs at low risk of bias for random sequence generation and allocation concealment, as allocation was decided using a computerized randomization algorithm (Corbel 2012; Kafy 2017; Loha 2019; Pinder 2015; Protopopoff 2018; West 2014), or by drawing lots at a public ceremony (Chaccour 2021). One cRCT was at unclear risk of bias because the randomization procedure was not described (Keating 2011).

Blinding

Due to the nature of the IRS application, blinding of participants and study personnel was not possible. Participant and personnel knowledge of the intervention was not expected to have an influence on the outcomes included in this review.

One study blinded microscopists (Pinder 2015). However, all studies measured prevalence using either an RDT or blood smear examination. As these tests are objective, all seven studies were at low risk of detection bias. Two studies that measured malaria incidence depended on self-reporting of fever, and as such the detection of this outcome may have been influenced by the participants' knowledge of the intervention (Corbel 2012; Pinder 2015). However, parasitaemia was confirmed using objective tests, and the study was, therefore, assessed as at unclear risk of bias.

Incomplete outcome data

One study reported a difference of more than 10% between the intervention and control arms in person-days that were lost to follow-up (Corbel 2012). This was judged at high risk of bias. Five studies had equivalent loss to follow-up in intervention and control arms and were, therefore, at low risk of bias (Chaccour 2021; Keating 2011; Pinder 2015; Protopopoff 2018; West 2014). One study did not report numbers lost to follow-up, but the authors stated that participants leaving the study area or moving homes between intervention and control arms were recorded and followed up to minimize the risk of attrition bias (Loha 2019). Therefore, the study was also considered at low risk of bias for this outcome. The remaining study did not report numbers lost to follow-up or describe efforts to mitigate for this and was, therefore, considered at unclear risk of bias (Kafy 2017).

Selective reporting

The studies reported on each of their intended outcomes as specified in their registered protocols (low risk of reporting bias).

Other potential sources of bias

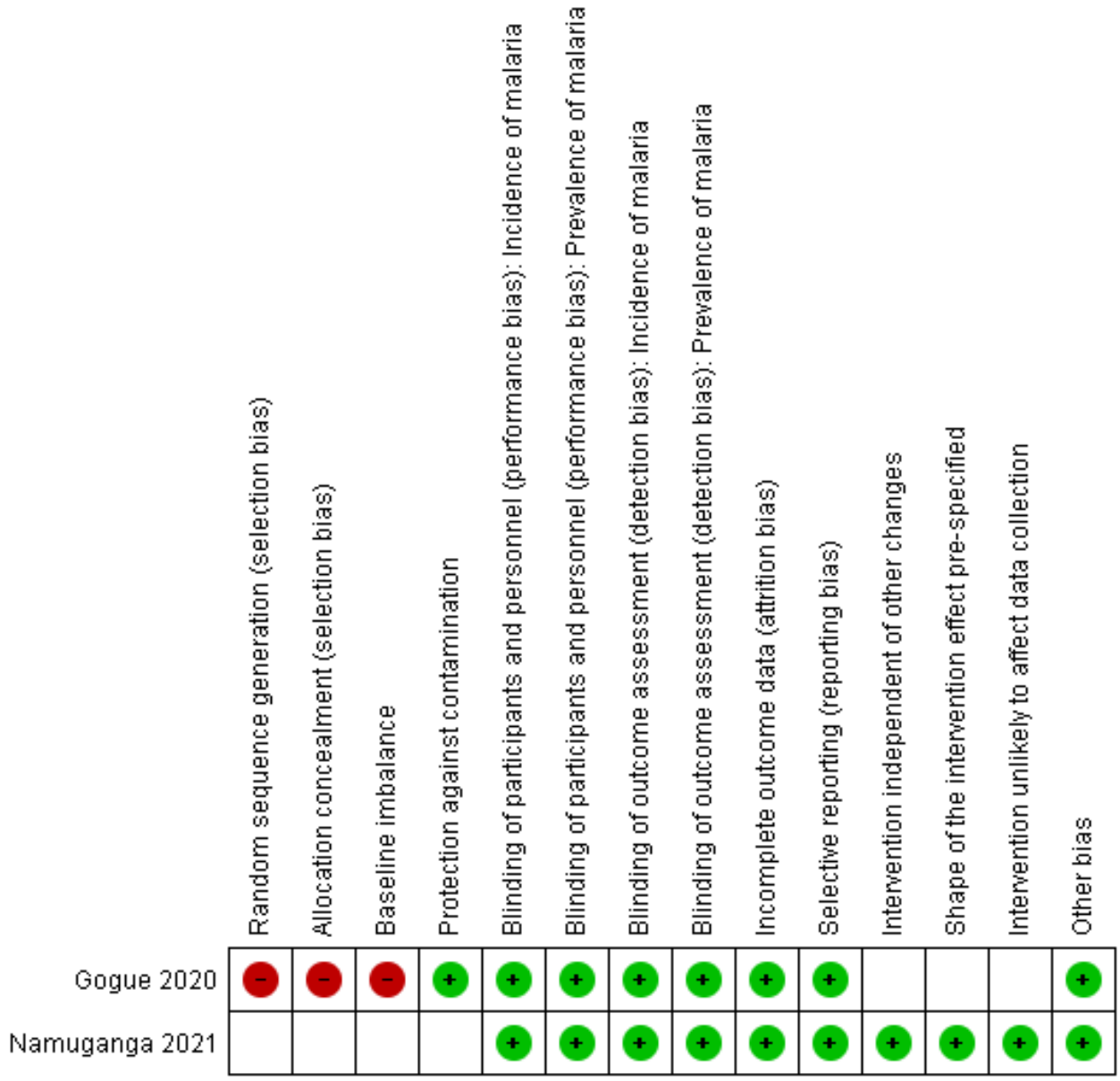
One study was at high risk of bias for incorrect analysis for the outcome of malaria parasite prevalence (Corbel 2012), due to concerns about repeated sampling of the same population leading to artificially narrower CIs for estimates of prevalence. To measure prevalence, the study authors conducted 12 cross-sectional surveys at six-week intervals, and reported the cumulative prevalence from across these 12 surveys, so that the unit of analysis was blood thick films rather than participants. The total number of registered children in the intervention villages was 890 and in control villages was 920, but the cumulative prevalence and 95% CI were calculated from sample sizes of 3649 in intervention villages and 4033 in control villages. This will result in narrower CIs for the RR estimate than would have been observed had the population been sampled once, introducing a bias in the meta-analysis that exaggerated the weight of this study. Furthermore, Corbel 2012 was at high risk of bias for baseline imbalance, as the prevalence of malaria was significantly higher in the intervention group than control group at baseline ($P < 0.01$).

None of the studies were at risk of recruitment bias as the study participants were randomly selected. One study was at unclear risk of baseline imbalance, as the baseline data for prevalence were not reported (Keating 2011). No studies were at high or unclear risk of bias from loss of clusters or other biases.

Risk of bias in quasi-experimental design studies

Randomization and allocation concealment are not applicable to Namuganga 2021 due to its ITS design. Gogue 2020 was at high risk of bias for these criteria due to its CBA design and because it was stated that districts were selected for IRS based on malaria burden and technical feasibility. Besides these inherent risks of bias, the two quasi-experimental design studies were well-designed with few other concerns over risk of bias (Figure 3).

Figure 3. RIsk of bias (quasi-experimental design studies): summary of review authors' judgements about each risk of bias item.



Due to the nature of the IRS application, blinding of participants and study personnel was not possible. Participant and personnel knowledge of intervention arm was not expected to have an influence on the objectively measured outcomes included in this review, and both studies were consequently considered at low risk of performance and detection bias. Both studies were also considered to be at low risk of attrition bias and selective reporting.

Gogue 2020 was at high risk of baseline imbalance as it was stated that districts malaria burden was higher in the arm receiving IRS. Namuganga 2021 was at low risk for each of the biases specifically relating to ITS design studies, as no other changes besides the introduction of IRS were implemented during the study period, the point of analysis was the time point that IRS was introduced, and the methods of data collection were the same before and after the intervention.

Effects of interventions

See: **Summary of findings 1** Non-pyrethroid-like indoor residual spraying (IRS) plus insecticide-treated nets (ITNs) versus ITNs alone for preventing malaria; **Summary of findings 2** Pyrethroid-like indoor residual spraying (IRS) + insecticide-treated nets (ITNs) versus ITNs alone for preventing malaria

Comparison 1: adding indoor residual spraying using non-pyrethroid-like insecticides to insecticide-treated nets

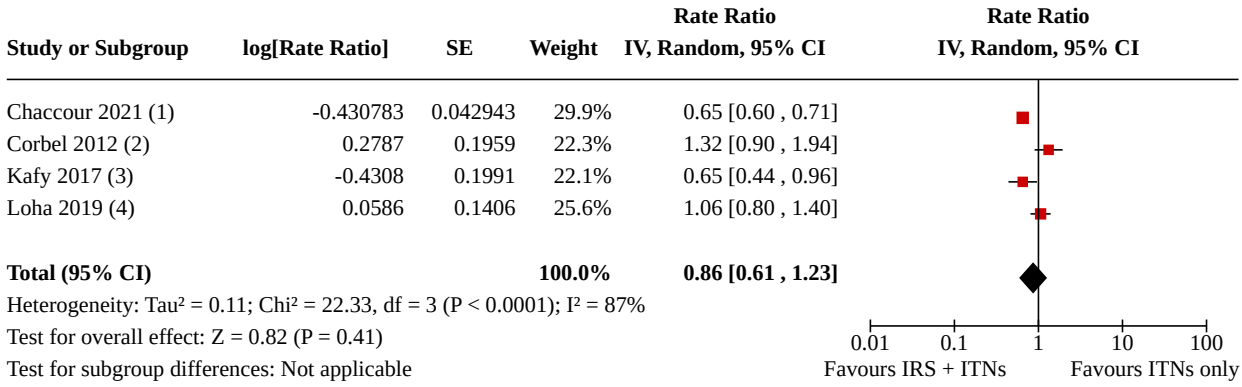
Eight studies investigated IRS using non-pyrethroid-like insecticides (Chaccour 2021; Corbel 2012; Gogue 2020; Kafy 2017;

Loha 2019; Namuganga 2021; Protopopoff 2018; West 2014). See Summary of findings 1.

Malaria incidence

Four cRCTs reported malaria incidence (Chaccour 2021; Corbel 2012; Kafy 2017; Loha 2019). Two studies reported a substantial benefit of IRS (Chaccour 2021; Kafy 2017), while two reported a slightly higher malaria incidence in the intervention arm (Corbel 2012; Loha 2019). This lack of consistency was reflected in the considerable heterogeneity (I^2 = 87%). Overall, the pooled analysis showed IRS may reduce malaria incidence (rate ratio 0.86, 95% CI 0.61 to 1.23; 4 cRCTs, 323,631 child-years; Analysis 1.1; low-certainty evidence; Figure 4).

Figure 4. Forest plot of comparison: 1 Non-pyrethroid-like indoor residual spraying (IRS) plus insecticide-treated nets (ITNs) versus ITNs alone, outcome: 1.1 Malaria incidence.



Footnotes

(1) IRS with pirimiphos-methyl
(2) IRS with bendiocarb
(3) IRS with bendiocarb (years 2 and 3)
(4) IRS with propoxur

We conducted a subgroup analysis by ITN usage, but this did not explain the heterogeneity observed between the studies (Analysis 1.2). Although the analysis showed that an effect was observed in each of the cRCTs with high ITN usage, while no effect was observed in the one cRCT with low ITN usage, this is counter-intuitive, as IRS may be expected to have a greater impact on malaria transmission where ITNs are not being used. Of note, Loha 2019 was excluded from this subgroup analysis as it did not report ITN usage using a measurement that was comparable to the other studies. However, the use of ITNs in the study was also low and declined throughout the study. The proportion of houses where at least one individual had used an ITN the previous night fell from between 47% to 49% in the first 26 weeks of the study period to just 1% between weeks 79 and 121. Further subgroup analyses by IRS coverage and malaria transmission setting (seasonal/perennial) also failed to explain the cause of the heterogeneity.

A sensitivity analysis excluding Corbel 2012, the only study considered to have any high risks of bias, did not cause any significant changes to the results of the pooled analysis (Analysis 1.3), and, therefore, we did not exclude the study from the analysis.

The results from Kafy 2017 were noteworthy: the data from different years of the study appeared in both Comparison 1 and Comparison 2. The first year had shown the addition of IRS using a pyrethroid-like insecticide had no effect on malaria incidence (rate ratio 1.00, 95% CI 0.36 to 2.78); in the second and third years, when a non-pyrethroid-like insecticide was used for IRS, there was a lower malaria incidence in the IRS arm (rate ratio 0.65, 95% CI 0.44 to 0.96).

Malaria incidence data from the two quasi-experimental design studies are presented in Table 6. After four to five years of sustained IRS, Namuganga 2021 reported a dramatic reduction in the monthly number of cases of malaria per person relative to the pre-intervention period (rate ratio 0.15, 95% CI 0.12 to 0.18). Gogue 2020 also reported a significant effect of IRS, with a difference-in-differences in cumulative malaria incidence across the six-month peak malaria season between the IRS and non-IRS arms of 37% (95% CI 18% to 57%).

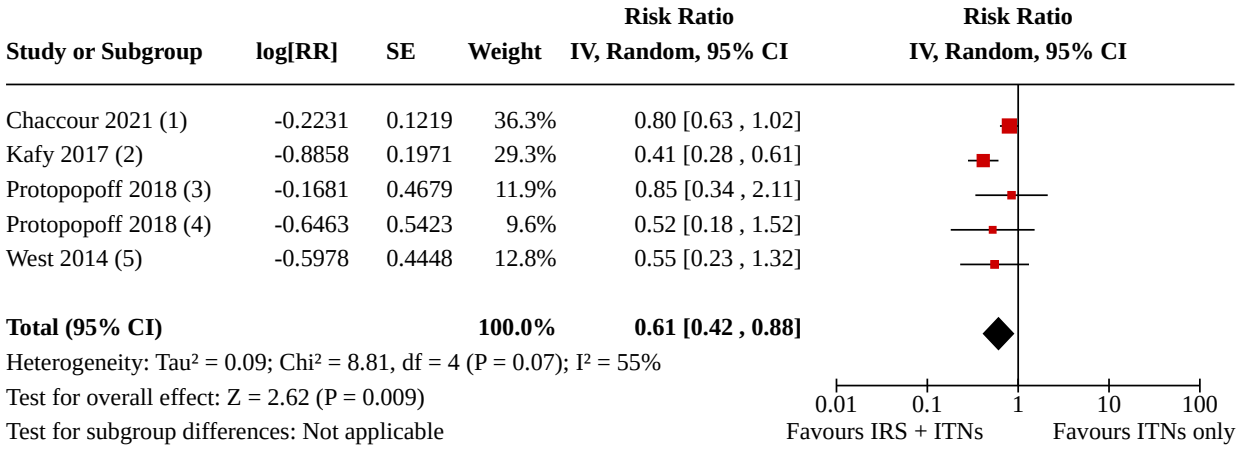
Malaria parasite prevalence

Five cRCTs assessed the effect of IRS on malaria parasite prevalence. Four cRCTs showed a benefit of IRS with substantial reductions in prevalence. However, in one cRCT, the point estimates tended towards a higher prevalence in the IRS arm (25.6%; 95% CI 21.0% to 30.2%) than the control arm (19.5%; 95% CI 16.6% to 22.5%), with no difference demonstrated on statistical testing (Corbel 2012).

Across the included studies, the pooled analysis showed IRS was associated with a reduction in malaria parasite prevalence (RR 0.72, 95% CI 0.47 to 1.11; 5 cRCTs, Analysis 1.4). However, a sensitivity analysis excluding Corbel 2012, a study with two high risk of bias concerns relating to this outcome, led to significant changes in the results of the pooled analysis and, therefore, we excluded the

results of this study from the analysis. Overall, after the exclusion of Corbel 2012, the pooled analysis showed IRS was associated with a large reduction in malaria parasite prevalence (RR 0.61, 95% CI 0.42 to 0.88; 4 cRCTs; 16,394 participants; Analysis 1.5; high-certainty evidence; Figure 5).

Figure 5. Forest plot of comparison: 1 Non-pyrethroid-like indoor residual spraying (IRS) plus insecticide-treated nets (ITNs) versus ITNs alone, outcome: 1.5 Malaria parasite prevalence (sensitivity analysis: exclusion of studies with high risk of bias; 1 study excluded; Corbel 2012).



Footnotes

(1) IRS with pirimiphos-methyl
(2) IRS with bendiocarb (years 2 and 3)
(3) [Comparator: pyrethroid-piperonyl butoxide net] IRS with pirimiphos-methyl
(4) [Comparator: pyrethroid ITNs] IRS with pirimiphos-methyl
(5) IRS with bendiocarb

One study provided two comparisons to the analysis, one comparing standard ITNs plus IRS versus standard ITNs alone, and one comparing pyrethroid-PBO nets plus IRS versus pyrethroid-PBO nets alone (Protopopoff 2018). In the comparison with standard ITNs, the addition of IRS was associated with a lower point estimate in malaria parasite prevalence (RR 0.52, 95% CI 0.18 to 1.52). In the comparison with PBO nets, the direction of effect was the same (RR 0.85, 95% CI 0.34 to 2.11). However, both analyses were underpowered and the confidence intervals included no effect. The smaller difference between the intervention and control arms in the second comparison may be explained by the improved effectiveness of pyrethroid-PBO nets over standard ITNs seen in the study. Even in the absence of IRS, the pyrethroid-PBO net arm had a prevalence of 31%, compared to 55% in the standard ITN arm.

Again, the results from Kafy 2017 were noteworthy: the data from different years of the study appeared in both Comparison 1 and Comparison 2. In the first year, following IRS implementation using a pyrethroid-like insecticide, the point estimate tended towards higher prevalence in the IRS arm, with no difference demonstrated on statistical testing (RR 1.96, 95% CI 0.86 to 4.46). However, in the second and third years, when a non-pyrethroid-like insecticide was used for IRS, there was a large reduction in prevalence (RR 0.41, 95% CI 0.28 to 0.61).

Entomological inoculation rate

Four studies reported estimates of the EIR (Chaccour 2021; Corbel 2012; Protopopoff 2018; West 2014). Due to considerable differences between studies in the way the EIR was defined and estimated, and in the effect sizes reported, it was not possible to conduct a meta-analysis. We presented the results of each study in Table 7.

In summary, in two of the four studies, the point estimates tended towards a reduction in EIR when IRS was added, but both analyses were underpowered and the confidence intervals included no effect. In the remaining two trials, little or no difference was observed. The results correlated with the reported epidemiological outcomes in three of the four studies.

- Chaccour 2021 reported mean values for the number of infected bites per household per year that tended towards a reduction when IRS was added (0.28, 95% CI 0.08 to 0.60) compared to the control arm (0.57, 95% CI 0.28 to 1.00). This was concordant with the results the study reported for epidemiological outcomes.
- Corbel 2012 reported the mean value for the number of infected bites per person per year when IRS was added (7.3, 95% CI 3.8 to 14.2) and in the control arm (9.4, 95% CI 5.1 to 17.1). This minor difference was concordant with the results the study reported for epidemiological outcomes, where there was no evidence of a lower malaria incidence or parasite prevalence in the combined arm.

- In both comparisons of Protopopoff 2018, there was a much lower mean EIR when IRS was added to nets. Similarly to the above epidemiological outcomes, the lower EIR was more marked in the comparison with the standard ITNs; whereas the EIR in the ITN-only arm was much lower with the pyrethroid-PBO net arm. We could not calculate CIs as the standard errors were not given for the means.
- West 2014 reported no reduction in the mean number of infected bites per household per month when IRS was added to ITNs (1.1, 95% CI 0.4 to 2.8 in the ITN-only arm versus 1.3, 95% CI 0.4 to 4.4 in the IRS plus ITNs arm). This finding was inconsistent with the epidemiological outcomes, where the study reported a large reduction in both malaria parasite prevalence and anaemia prevalence.

Sporozoite rate

Two studies reported the effect on the sporozoite rate (Protopopoff 2018; West 2014). Both defined this outcome as the proportion of *An gambiaes.l.* caught from light traps with sporozoites. Table 8 summarizes the characteristics and effects of all studies reporting the sporozoite rate included in this review.

- In both comparisons of Protopopoff 2018, the sporozoite rate was lower when IRS was added. In the IRS plus standard ITNs arm the proportion was 0.4% versus 2.8% in the standard ITNs alone comparison. In the IRS plus pyrethroid-PBO net arm, the proportion was 0% versus 0.7% in the pyrethroid-PBO net alone comparison. The study did not report 95% CIs for these measurements or an overall effect estimate.
- West 2014 reported a 28% reduction in the odds of a mosquito being infected with sporozoites in the intervention arm compared to the control arm, but the CI included no effect (OR 0.72, 95% CI 0.21 to 2.53).

Adult mosquito density

Four studies reported the adult mosquito density as the number of adult mosquitoes caught per trap per night (Chaccour 2021; Loha 2019; Protopopoff 2018; West 2014). One study measured adult mosquito density as a biting rate (Corbel 2012), Loha 2019 additionally reported the indoor resting density (number of mosquitoes per house per night) and outdoor resting density (number of mosquitoes caught per artificial outdoor pit shelter per day). Namuganga 2021 reported a human biting rate, calculated as the number of female *Anopheles* mosquitoes captured per house per night. Differences in the measurement and reporting of these outcomes precluded a quantitative synthesis. Table 9 summarizes the characteristics and effects of all studies reporting adult mosquito density included in this review.

In summary, five studies reported a reduction in adult mosquito density when IRS was added, and one study did not (Loha 2019). In each case, the results correlated with the reported epidemiological outcomes.

- Chaccour 2021 reported a reduction of approximately 50% in mosquitoes caught per trap per night in the intervention arm compared to the control arm (rate ratio 0.52, 95% CI 0.41 to 0.67).
- Corbel 2012 reported a reduction of bites by 31% in the intervention arm compared to the control arm, but the CIs were wide and included no effect (rate ratio 0.69, 95% CI 0.38 to 1.25).
- Loha 2019 reported the indoor resting density was significantly higher in the IRS arm (0.34, 95% CI 0.24 to 0.47) than the control arm (0.06, 95% CI 0.03 to 0.12). Similar, the outdoor resting density was higher in the IRS arm (0.43, 95% CI 0.27 to 1.69) than the control arm (0.04, 95% CI 0.01 to 0.15).
- Namuganga 2021 reported a dramatic reduction in human biting rate from 18.71 female *Anopheles* per house per night in the control arm to 3.23 in the intervention arm (rate ratio 0.29, 95% CI 0.17 to 0.50).
- In the IRS plus standard ITNs versus standard ITNs alone comparison, Protopopoff 2018 reported a mean number of 2.37 vectors caught per night per household in the intervention arm and 2.83 vectors per night per household in the control arm. In the IRS plus pyrethroid-PBO nets arm, the mean number was 1.85 versus 1.84 in the pyrethroid-PBO nets alone comparison. The study did not report 95% CIs for these measurements or an overall effect estimate.
- West 2014 reported a 77% reduction of adult mosquitoes in the intervention arm compared to the control arm, but the CIs included no effect (rate ratio 0.23, 95% CI 0.04 to 1.44).

Anaemia prevalence

Three studies assessed the effect on anaemia prevalence. One study provided two comparisons to the analysis, one comparing standard ITNs plus IRS versus standard ITNs alone, and one comparing pyrethroid-PBO nets plus IRS versus pyrethroid-PBO nets alone. Similarly to the previous outcomes, the introduction of IRS with a standard ITN was associated with a reduction in the prevalence of anaemia compared to a standard ITN alone (RR 0.17, 95% CI 0.04 to 0.67), but the combination of IRS plus pyrethroid-PBO net was not favourable to a pyrethroid-PBO net alone (RR 1.18, 95% CI 0.09 to 15.08). Of the remaining two studies, neither West 2014 (RR 0.63, 95% CI 0.35 to 1.14) nor Loha 2019 (RR 0.94, 95% CI 0.72 to 1.22) showed a significantly reduced anaemia prevalence when IRS was added .

Across the included studies, the pooled analysis showed that the prevalence of anaemia may be lower when IRS is added to communities using ITNs (RR 0.71, 95% CI 0.38 to 1.31; 3 cRCTs, 4288 participants; Analysis 1.6; low-certainty evidence), and the meta-analysis showed moderate heterogeneity between studies (I^2 = 49%). A subgroup analysis by ITN usage did not resolve this heterogeneity (Analysis 1.7). All studies achieved high coverage of IRS and, therefore, we did not perform a subgroup analysis by this metric.

Level of insecticide resistance

Corbel 2012 reported the allelic frequency of 1014F kdr, a genetic marker associated with resistance to pyrethroid insecticide in mosquitoes. There was no difference detected in the frequency of 1014F kdr in the IRS plus ITNs arm (86%, 95% CI 80% to 92%) compared to the ITN-only arm (86%, 95% CI 79% to 93%). The study did not report the individual frequency in each intervention arm of G119S ace1, a genetic marker associated with resistance to carbamate insecticides. However, it commented that the allele was almost absent across the study area during the study (less than 5%, 2123 participants). Kafy 2017 reported that there was less phenotypic pyrethroid resistance in the IRS plus ITNs arm, with 68% mosquito mortality after exposure to deltamethrin (95% CI 60.0% to 76.0%) compared to 56.1% mortality in the ITN-only arm (95% CI 47.1% to 64.9%). Loha 2019 reported that, during the study

period, the was no change in the primary vector's susceptibility to pyrethroids or the carbamate insecticides used for IRS.

Comparison 2: adding indoor residual spraying with pyrethroid-like insecticides to insecticide-treated nets

Three studies investigated IRS using pyrethroid-like insecticides (Kafy 2017; Keating 2011; Pinder 2015). See Summary of findings 2.

Malaria incidence

The two studies that reported the effect on malaria incidence found no evidence of an effect of IRS in communities that were using ITNs (rate ratio 1.07, 95% CI 0.80 to 1.43; 2 cRCTs, 15,717 child-years; Analysis 2.1; moderate-certainty evidence).

Malaria parasite prevalence

The three studies that reported the effect on malaria parasite prevalence found no evidence of an effect of IRS in communities that were using ITNs, with no heterogeneity between the studies (RR 1.11, 95% CI 0.86 to 1.44; 10,820 participants; Analysis 2.2; moderate-certainty evidence).

Entomological inoculation rate

One study reported the effect on the estimated EIR (Pinder 2015). The authors defined the estimated EIR as the mean number of infected bites per person per transmission season. In the first year, the study reported a difference in the estimated EIR of 2.44 (95% CI 0.69 to 6.39) without IRS and 1.08 (95% CI 0.16 to 4.02) when IRS was added, but the CIs overlapped. The pattern in the point estimates was the same in the second year, with an estimated EIR of 1.45 (95% CI 0.15 to 5.69) without IRS and 0.29 (95% CI 0.00 to 2.66) when IRS was added. While the point estimates were not consistent with the human data, the wide CIs make no inference possible. Table 7 summarizes the characteristics and effects of all studies reporting the EIR included in this review.

Sporozoite rate

One study reported the effect on the sporozoite rate (Pinder 2015). The authors defined this as the proportion of *An gambiaes.l.* caught using light traps, with sporozoites. The actual number of infected mosquitoes detected was small (19 in both arms across the two years). In the first year of assessment, 0.19% (4/2131) of *An gambiae s.l.* were positive in the intervention arm and 0.32% (9/2829) were positive in the control arm. The risk of a mosquito being infected with sporozoites was 41% lower in the intervention arm compared to the control arm, but the analysis was underpowered (RR 0.59, 95% CI 0.18 to 1.91). In the second year of assessment, 0.65% (5/773) of *An gambiae s.l.* were positive in the intervention arm and 0.09% (1/1131) in the control arm. The risk of a mosquito being infected with sporozoites was more than seven times higher in the intervention arm compared to the control arm, but again this was underpowered (RR 7.32, 95% CI 0.86 to 62.5). Table 8 summarizes the characteristics and effects of all studies reporting the sporozoite rate included in this review.

Adult mosquito density

One study reported the effect on adult mosquito density (Pinder 2015). The authors defined this outcome as the number of *An gambiae s.l.* per trap per night. The study used both light and exit traps. There were no clear differences between the arms, and the CIs were wide (2010 using light traps: MD −1.22, 95% CI −3.58 to 1.14; 2010 using exit traps: MD −0.13, 95% CI −0.54 to 0.28; 2011 using light traps: MD −0.69, 95% CI −2.15 to 0.77; and 2011 using exit traps: MD −0.40, 95% CI −1.05 to 0.25). Table 9 summarizes the characteristics and effects of all studies reporting adult mosquito density included in this review.

Anaemia prevalence

The one study that reported the prevalence of anaemia found no evidence of an effect of IRS in communities that were using ITNs (RR 1.12, 95% CI 0.89 to 1.40; 4186 participants, 1 cRCT; Analysis 2.3; low-certainty evidence).

Level of insecticide resistance

No studies reported level of insecticide resistance in such a way that an effect size could be calculated. However, Kafy 2017 reported that in the first year of the study there was no difference in mosquito deltamethrin mortality when IRS was added (65%, 95% CI 49% to 81%) compared to the control arm (60%, 95% CI 44% to 76%).

DISCUSSION

Summary of main results

In communities using ITN, adding IRS with a non-pyrethroid-like insecticide may reduce malaria incidence on average, although there was qualitative heterogeneity between studies and it may be that the intervention is not always effective. IRS with a non-pyrethroid-like insecticide also appeared to reduce malaria parasite prevalence. However, the high certainty of this result depended on the exclusion of a study that was considered to be at high risk of bias for this outcome.

No additional benefit of adding IRS using a pyrethroid-like insecticide to ITNs was detected for malaria outcomes. For both comparisons included in this review, entomological outcomes were reported inconsistently, and qualitative comparisons with the human malaria outcomes showed mixed correlation in relation to the presence or absence of an effect.

Overall completeness and applicability of evidence

There are two main reasons why the use of IRS in addition to ITNs may be a preferred policy option to the use of ITNs alone. First, it may improve malaria control simply because two interventions are better than one. Second, the addition of IRS may compensate for lower efficacy of ITNs due to pyrethroid resistance. Our review attempted to explore the relative importance of these two potential benefits by presenting separate analyses dependent on the target site of the insecticides used for IRS.

The rationale behind this was that if pyrethroid resistance is causing ITNs to fail, introducing a pyrethroid-like IRS will be unlikely to have a benefit. The included studies that used pyrethroid-like insecticides for IRS followed this rationale, showing no effect on epidemiological outcomes. In contrast, introducing a non-pyrethroid-like IRS should improve malaria disease outcomes, particularly in areas where vectors are resistant to pyrethroid insecticides. While the included studies that used non-pyrethroid-like insecticides did demonstrate a reduction in epidemiological outcomes on average, this effect was not always observed. More research will be needed to understand this heterogeneity in order to predict when and where the combination of IRS and ITNs will not have an impact.

A third justification for combining a non-pyrethroid-like IRS with ITNs is to restore susceptibility to pyrethroids in the vector or slow the emergence of resistance in the first place (WHO 2012). By this rationale, waiting to implement the combination of IRS with ITNs until incremental impact is demonstrated over ITNs alone may mean doing so far too late (Killeen 2018). While many studies characterized insecticide resistance (either phenotypically, genotypically, or both) at the start of the follow-up period, only three studies continued to monitor the changes in insecticide resistance beyond the intervention roll-out, though each used different outcomes to measure this (Corbel 2012; Kafy 2017; Loha 2019). Consequently, we were unable to adequately explore the effect that mass roll-out of both core interventions would have on insecticide resistance. While standardized methods of measuring and reporting insecticide resistance would help to compare these results between studies, it remains a matter of conjecture whether a considerable change in resistance would be detected within the period of a typical RCT.

Given the wide geographical variety of malaria endemicities, transmission patterns, and insecticide resistance, we need to be cautious with inferences to policy from the limited number of studies conducted to date. Applicability of vector control interventions in different settings is always a point for discussion, as the ecology, behaviour, and insecticide-resistance profiles of *Anopheles* mosquitoes can vary massively between and within species. The included studies in this review were all conducted in Sub-Saharan Africa and the majority were conducted in areas where the primary vector species was *An gambiae s.s. or An funestus*, two highly anthropophagic and endophagic vectors that are potentially more susceptible to both IRS and ITNs (Okumu 2011). The partially zoophagic and exophagic vector *Anopheles arabiensis* acted as the primary vector in two studies (Kafy 2017; Loha 2019), and as a secondary vector in a further two studies (Namuganga 2021; West 2014). The effect of combining IRS with ITNs in the studies reported here will not necessarily apply to other target species in other settings, particularly those which are highly exophilic and exophagic.

Quality of the evidence

Details of the downgrading for GRADE are presented in Summary of findings 1 and Summary of findings 2.

Adding IRS using a non-pyrethroid-like insecticide to ITNs may reduce malaria incidence (low-certainty evidence). While four included studies showed a beneficial effect of IRS on malaria incidence, two included studies showed no effect, leading to imprecision and inconsistency in the results. This decreased the certainty of the evidence and raised doubts about the generalizability to other settings. We found evidence that IRS using a non-pyrethroid-like insecticide reduces malaria parasite prevalence (high-certainty evidence).

Adding IRS using a pyrethroid-like insecticide to ITNs provided no improvement in malaria outcomes across the three studies (low- to moderate-certainty evidence).

For both comparisons included in this review, entomological outcomes were reported inconsistently, and consequently we do not know whether IRS with either non-pyrethroid-like or pyrethroid-like insecticides affect entomological indicators of malaria (very low-certainty evidence)

Potential biases in the review process

As not all the included studies used standardized measures of ITN ownership and use, we were unable to directly compare these metrics between each of the studies. Any comparisons made between studies that used different measurements to one another are limited. The exclusion of certain studies that did not use standardized measurements reduce our understanding of the effect of IRS at high, moderate, or low ITN ownership and use. In future studies, the use of consistent measurements that follow defined criteria would alleviate this issue for later updates of the review.

We attempted to subgroup studies based on seasonal, perennial, or epidemic malaria transmission status, as per the review protocol, and this variable was not found to influence the effect of IRS. However, as all the study countries experience annual variation in transmission and epidemics can occur in areas with seasonal or perennial transmission, assigning study areas to single categories is challenging, and the value of comparisons made between these categories is, therefore, somewhat limited. In future updates to this review, a comparison between study areas of high or low transmission following WHO defined criteria may be more appropriate.

In order to include data from as many studies as possible into the meta-analysis for malaria parasite prevalence, we converted the adjusted odds ratios reported in five studies into adjusted RRs. This conversion assumes that all subjects have the same outcome risk when not exposed and that all subjects experience the same change in outcome odds when exposed. Consequently, there is a risk that these conversions may lead to biased adjusted RRs where this is not the case.

Agreements and disagreements with other studies or reviews

Two reviews have been conducted on this topic: a narrative review published by the WHO (WHO 2014a) and a systematic review (Sherrard-Smith 2018). The narrative review included the studies by Corbel 2012, Pinder 2015, and West 2014 (WHO 2014a) and concluded that West 2014, the only study of the three to show a reduction in malaria epidemiological outcomes favouring the intervention, differed from the other studies because the study area had low ITN usage, which the implementation of IRS compensated for. However, our review includes several studies that show a reduction in epidemiological outcomes even in areas with high ITN usage. Whether or not the IRS was conducted using a pyrethroid-like insecticide appears to be a better predictor for success or failure of the intervention, although there remains some heterogeneity when a non-pyrethroid-like insecticide is used.

The systematic review meta-analyzed results from experimental hut studies and found that IRS substantially reduced entomological indicators of malaria in these types of studies (Sherrard-Smith 2018). The review also utilized a malaria transmission model incorporating this data to determine the impact on epidemiological indices, concluding that the impact of IRS was highly dependent on bednet use, seasonality, endemicity, and pyrethroid resistance status of local mosquito populations. Our review could not confirm an impact of IRS on entomological outcomes, and does not conclusively show whether bednet use or seasonality of malaria have any impact on the efficacy of IRS.

AUTHORS' CONCLUSIONS

Implications for practice

With the evidence to date, in communities using ITNs, IRS with a non-pyrethroid insecticide appears to reduce malaria parasite prevalence and may also reduce malaria incidence on average, but this effect was not always present. These benefits have not been observed when using a pyrethroid-like insecticide. The evidence from these studies was insufficient to evaluate whether adding IRS in communities using ITNs would be an effective strategy to prevent pyrethroid resistance emerging.

Implications for research

There was unexplained qualitative heterogeneity between studies examining IRS using non-pyrethroid-like IRS. Consequently, there is uncertainty over whether this intervention will be effective in all settings, and other factors may influence its impact on malaria transmission. Researchers and policymakers may wish to consider pragmatic approaches to generate further evidence, such as programme implementation using stepped wedge designs and other quasi-experimental methods during programme implementation. Other sources of evidence such as modelling and entomological indices from experimental hut study designs may also help unpick where IRS is most likely to be effective. Standardization of measuring and reporting both entomological outcomes and insecticide resistance in efficacy studies would also help strengthen the evidence base and allow for better comparisons between studies.

ACKNOWLEDGEMENTS

The Academic Editor of this review update is Dr Patricia Graves.

We are also grateful for the mentorship of Professor Paul Garner, Cochrane Infectious Diseases Group (CIDG) Co-ordinating Editor and previous author of this review, and to Vittoria Lutje, Information Specialist with the CIDG, for help with the literature search strategy.

Joseph Pryce, Nancy Medley, and Leslie Choi are supported by the Research, Evidence and Development Initiative (READ-It). READ-It and the CIDG editorial base are funded by aid from the UK government for the benefit of low- and middle-income countries (project number 300342-104). The views expressed do not necessarily reflect the UK government's official policies.

Leslie Choi is supported by PIIVeC, the Partnership for Increasing the Impact of Vector Control. PIIVeC is funded by the Medical Research Council of the UK (grant number MR/P027873/1) through the Global Challenges Research Fund.

This work was partly supported through a grant from the Global Malaria Programme, WHO (WHO Global Malaria Programme Agreement for Performance of Work (APW) Grant 2017 (number 709319)). The views expressed in this review have not been influenced by, or necessarily reflect, WHO policy.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Chaccour 2021

Study characteristics	
Methods	**Study design:** 2-arm, open-label, parallel-arm, cRCT **Unit of allocation:** village. Villages not reaching the minimum population for inclusion were combined with the nearest neighbouring village to form a single cluster. **Number of units:** 168 clusters (84 IRS, 84 no IRS) were involved in the passive surveillance component of the study. 86 clusters (43 IRS, 43 no-IRS) participated in the active cohort component of the study. **Outcome assessment/surveillance type:** active surveillance of a cohort of children aged < 5 year (18 per cluster), passive surveillance of people of all ages through the national health system, and annual cross-sectional surveys near the peak of the transmission season (April–May). **Length of follow-up:** Not reported **Adjustment:** primary analysis was done on intention-to-treat basis, assuming that all individuals living in an IRS cluster received IRS in their household. The effect of IRS was estimated using negative binomial regression models with the GEE approach. Sensitivity analyses and additional per-protocol analysis adjustments were done considering ITN ownership and usage, household socioeconomic status, and cluster size (as defined by number of households).
Participants	**Number of participants:** 1536 (active cohort), 139,286 across 194 villages under passive surveillance **Inclusion criteria for participants:** children aged < 5 years (active cohort); all ages (passive surveillance and cross-sectional surveys)
Interventions	**IRS active ingredient and dosage:** pirimiphos-methyl – 1 g/m^2 Formulation: Actellic 300 CS Frequency of spraying: annually for 2 years Time of spraying: October–November 2016 and 2017 Spraying conducted by: President's Malaria Initiative Africa Indoor Residual Spraying (PMI AIRS) Coverage: all eligible structures (ones in which people slept and that had sprayable surfaces) Compliance: 83% of target buildings sprayed in 2016, 85% of targets sprayed in 2017 **LLIN** Active ingredient and dosage: alphacypermethrin (in 2017 distribution campaign) Time of implementation: mass distribution campaigns in 2013 and 2017 Coverage measure: ownership among all ages: 54% in 2017 and 95% in 2018 **Coverage in IRS arm:** Not reported **Coverage in control arm:** Not reported **Compliance measure:** usage in households owning ≥ 1 ITN: 89% in 2018. No differences between study arms in proportion of children aged < 5 years who were reported to have slept under a net the night before monthly study; implemented household surveys, with estimates ranging from 59% to 67% before the mass distribution campaign and from 92% to 94% after the campaign. **Cointerventions:** none described
Outcomes	• Malaria infection incidence in an active cohort of children aged < 5 years

Chaccour 2021 *(Continued)*

- Malaria case incidence in all ages through passive surveillance of national health system data (confirmed case defined as fever, either reported or measured plus a positive RDT)
- Malaria prevalence in all ages
- Adult mosquito density
- EIR

Location profile	**Study location:** Mopeia district, Zambezia province, Mozambique **Malaria endemicity:** highly endemic (> 60% parasite prevalence) **EIR:** < 1 Infectious bites per household per month ***Plasmodium* species:** *P falciparum*
Vector profile	**Primary (and secondary) vector species:***An funestus* and *An gambiae s.l.* **Phenotypic resistance profile:** resistant to pyrethroids (34–52% mortality after exposure to deltamethrin, 33–40% mortality after exposure to lambda-cyhalothrin) **Method of mosquito collection:** vector densities were monitored monthly in a subset of 10 sentinel study villages: 5 IRS and 5 no-IRS villages, using overnight CDC light trap collections in 8 houses per village and paired indoor–outdoor human landing collections at 1 house per village, for 3 nights each month (note: no analysis of HLC results. Rate ratios were calculated using CDC light trap data only).
Notes	For inclusion in the review meta-analyses, we calculated adjusted risk ratios for prevalence from the reported adjusted odds ratios following the methodology stated in Section 12.5.4.4 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011a).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Villages were randomized by drawing lots during a public community-engagement ceremony.
Allocation concealment (selection bias)	Low risk	Randomization procedure would not have been at risk of selection bias.
Blinding of participants and personnel (performance bias) Incidence of malaria	Low risk	Participants and personnel were not blinded to intervention. Low risk of bias for both incidence and prevalence because the outcomes measured were objective.
Blinding of participants and personnel (performance bias) Prevalence of malaria	Low risk	Participants and personnel were not blinded to intervention. Low risk of bias for both incidence and prevalence because the outcomes measured were objective.
Blinding of outcome assessment (detection bias) Incidence of malaria	Low risk	Participants and personnel were not blinded to intervention. Low risk of bias for both incidence and prevalence because the outcomes measured were objective.
Blinding of outcome assessment (detection bias) Prevalence of malaria	Low risk	Participants and personnel were not blinded to intervention. Low risk of bias for both incidence and prevalence because the outcomes measured were objective.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up was equivalent in both arms.

Chaccour 2021 *(Continued)*

Selective reporting (reporting bias)	Low risk	All outcomes stated in the protocol were reported.
Recruitment bias	Low risk	Low risk as incidence data were collected through passive surveillance and active cohorts were randomly recruited.
Loss of clusters	Low risk	No loss of clusters.
Baseline imbalance	Low risk	No major differences in terms of distance to the nearest health facility from the cluster's centroid, ITN ownership, basic socioeconomic characteristics, age, or gender of the children enrolled. Baseline data suggested mosquito density was significantly higher in the intervention group prior to IRS.
Incorrect analysis	Low risk	No incorrect analysis.
Comparability with RCTs randomizing participants	Low risk	Estimates were adjusted for clustering.
Other bias	Low risk	No other biases identified.

Corbel 2012

Study characteristics	
Methods	**Study design:** cRCT with 4 intervention arms: • Targetted LLIN (TLLIN): one ITN per sleeping unit of pregnant women or children < 6 years old • TLLIN + full coverage of carbamate IRS (TLLIN + IRS) • Universal LLIN (ULLIN): one ITN per sleeping unit • ULLIN plus full coverage of CTPS (ULLIN + CTPS) The relevant comparison for this review was TLLIN vs TLLIN + IRS **Unit of allocation:** village **Number of units:** 7:7:7:7 **Outcome assessment/surveillance type:** 60 children were randomly selected from each village to participate in the study. Active case detection during 12 surveys at 6-week intervals. Thick blood films were taken from every sick child. Cross-sectional surveys were done at each period of clinical monitoring, including every symptomatic child. Mosquitoes were collected during 8 surveys at 6-week intervals. Sporozoite rate was detected using ELISA of heads and thoraces for *P falciparum* CSP. **Length of follow-up:** 18 months (June 2008 to December 2009) **Adjustment:** outcomes were compared between the treatment and control groups, taking into account the effect of age and the sampling design in Poisson, logistic, and linear multivariate regression models using a generalized estimating equations approach.
Participants	**Number of participants:** 413 (TLLIN + IRS); 429 (TLLIN) **Population characteristics** **Inclusion criteria for participants:** children aged < 6 years from villages that had moderate pyrethroid resistance – *kdr* allelic frequency > 40%, a population of 250–500, and no local health centre. **Withdrawal and loss to follow-up:** in every group, about 20% of the recordings were not taken into account because of loss to follow-up (17%), death of children (1.5%), and refusal (1.5%).

Corbel 2012 *(Continued)*

Interventions	**IRS** Active ingredient and dosage: bendiocarb, 400 mg/m² Formulation: 80% wettable powder (FICAM 80, Bayer) Frequency of spraying: every 8 months Time of spraying: June 2008 to December 2009 Coverage: aimed for 80% Buffer size between clusters: at least 2 km **TLLIN** Active ingredient and dosage: deltamethrin; 55 mg AI per m² Formulation: PermaNet 2.0 Coverage: 1 LLIN was provided per sleeping unit of children aged < 6 years or pregnant women, or both. This corresponds to a mean of 1 LLIN every 4 people. Compliance: 43% (95% CI 40 to 45) **Control** TLLIN only (details same as above) **Cointerventions:** none described
Outcomes	• Incidence density rate of *P falciparum* malaria in children aged < 6 years (defined as malaria symptoms plus a parasite density > 2000 parasites/µL) • Prevalence in children aged < 6 years • EIR • Human biting rate • Prevalence of pyrethroid resistant 1014F *kdr* allele in malaria vectors • Geometric mean of *P falciparum* parasites per µL
Location profile	**Study location:** Ouidah-Kpomassè-Tori Bossito, southern Benin **Malaria endemicity:** perennial, low **EIR:** Not reported **Population proximity/density:** Not reported
Vector profile	**Primary (and secondary) vector species:***An gambiae* (primary), *An funestus* (secondary) **Vector behaviour (nature, stability, adult habitat, peak biting times, exophilic/endophilic, exophagic/endophagic, anthropophilic/zoophilic):** Not reported **Phenotypic resistance profile:** Not reported **Genotypic resistance profile:***kdr* allelic frequency < 40% **Method of mosquito collection:** indoor/outdoor human landing catches at 4 sites per village (10 pm to 6 am) for 2 consecutive nights per survey (i.e. 16 person-nights per village per survey)
Notes	For inclusion in the review meta-analyses, we calculated adjusted risk ratios for prevalence from the reported adjusted odds ratios following the methodology stated in Section 12.5.4.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a).

Corbel 2012 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "In each village, we randomly selected 60 children aged < 6 years from the census list of the inhabitants to participate using computer-generated random numbers. The allocation sequence and randomization of the blocks and children were prepared by the study statistician at IRD-CREC".
Allocation concealment (selection bias)	Low risk	Children and study investigators were not blinded to treatment allocation but allocation sequence and randomization of the blocks and children were prepared by the study statistician at IRD-CREC.
Blinding of participants and personnel (performance bias) Incidence of malaria	Low risk	Participants and personnel were not blinded to intervention.
Blinding of participants and personnel (performance bias) Prevalence of malaria	Low risk	Participants and personnel were not blinded to intervention. Low risk of bias for prevalence as all cohort members had their blood taken.
Blinding of outcome assessment (detection bias) Incidence of malaria	Unclear risk	Participants and personnel were not blinded to intervention. Unclear risk of bias for incidence due to self-reporting of sickness before confirmation by microscopy, an objective assessment.
Blinding of outcome assessment (detection bias) Prevalence of malaria	Low risk	Participants and personnel were not blinded to intervention. Low risk of bias for prevalence as all cohort members had their blood taken.
Incomplete outcome data (attrition bias) All outcomes	High risk	Loss to follow-up performed but > 10% difference in children-days between the 2 arms: 5224 theoretical children-days missing in control arm, 6688 children-days missing in intervention arm.
Selective reporting (reporting bias)	Low risk	All children-days were analyzed. The study protocol reported 1 each outcome as stated in the clinical trials register (note: retrospectively registered).
Recruitment bias	Low risk	Cohort of children were randomly selected using census data and computer generated numbers.
Loss of clusters	Low risk	No clusters were lost.
Baseline imbalance	High risk	Baseline data were displayed. There were no significant differences at baseline between intervention arms for incidence (P = 0.78). However, the prevalence was significantly higher in the TTLIN + IRS arm vs TTLLIN only (P = 0.01). Entomological outcomes were not provided at baseline.
Incorrect analysis	High risk	Adjustment for clustering was done. There were concerns about repeated sampling of the same population leading to artificially narrower confidence intervals for estimates of prevalence. To measure prevalence, the trial authors conducted 12 cross-sectional surveys at 6-weekly intervals, and appear to report the cumulative prevalence from across these 12 surveys, so that the unit of analysis is blood thick films rather than participants. The total number of registered children in the intervention and control villages were 890 and 920, respectively, but the cumulative prevalence and 95% CI are calculated from sample sizes of 3649 and 4033, respectively. This will result in narrower confidence intervals for the risk ratio

Corbel 2012 *(Continued)*

		estimate than would have been observed had the population been sampled once, introducing a bias in the meta-analysis that exaggerates the weight of this study.
Comparability with RCTs randomizing participants	Low risk	Because the intervention is expected to have community level impact as well as individual impact, cRCTs are the most appropriate study design to capture this.
Other bias	Low risk	No other biases.

Gogue 2020

Study characteristics	
Methods	**Study design:** retrospective controlled before-after following re-introduction of IRS to specific communities **Outcome assessment/surveillance type:** passive case surveillance using data extracted from district health information system **Length of follow-up:** pre-IRS: September 2016 to February 2017; post IRS: September 2017 to February 2018
Participants	**Number of participants:** 1,046,545, with 163,058 in IRS districts **Inclusion criteria for participants:** all residents of targeted areas eligible for inclusion
Interventions	**IRS** Active ingredient and dosage: pirimiphos-methyl Formulation: CS Frequency of spraying: once Time of spraying: August–September 2017 Coverage: targeted every eligible structure in included districts Compliance: 95.6–96.9% Time of implementation: mass campaign in 2014 Coverage: households owning ≥ 1 net in 2016: 93.9% Compliance: proportion using a net previous night in 2016: 75.5% (children aged < 5 years); 63.2% (all ages)
Outcomes	• Malaria incidence (number of RDT-positive results/total population)
Location profile	**Study location:** Upper East region, Northern Savannah, Ghana (note: other regions described in study did not meet inclusion criteria for this review) **Phenotypic resistance profile:** widespread pyrethroid resistance **Malaria endemicity:** high, perennial, and seasonal with peak transmission September–February. Malaria prevalence in 2014 by RDT 22.7%
Vector profile	**Primary (and secondary) vector species**: *An gambiaes.l.* and *An funestus*

Gogue 2020 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization.
Allocation concealment (selection bias)	High risk	No allocation concealment.
Blinding of participants and personnel (performance bias) Incidence of malaria	Low risk	Participants and personnel were not blinded to intervention. Low risk of bias for both incidence and prevalence because the outcomes measured were objective.
Blinding of participants and personnel (performance bias) Prevalence of malaria	Low risk	Participants and personnel were not blinded to intervention. Low risk of bias for both incidence and prevalence because the outcomes measured were objective.
Blinding of outcome assessment (detection bias) Incidence of malaria	Low risk	Participants and personnel were not blinded to intervention. Low risk of bias for both incidence and prevalence because the outcomes measured were objective.
Blinding of outcome assessment (detection bias) Prevalence of malaria	Low risk	Participants and personnel were not blinded to intervention. Low risk of bias for both incidence and prevalence because the outcomes measured were objective.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data likely to bias the results.
Selective reporting (reporting bias)	Low risk	No evidence that outcomes were selectively reported.
Baseline imbalance	High risk	Baseline outcome measurements not described but it is stated that districts were selected for IRS based on malaria burden and technical feasibility.
Protection against contamination	Low risk	Allocation was by community and it is unlikely that the control group received the intervention.
Other bias	Low risk	No other biases identified.

Kafy 2017

Study characteristics

Methods	**Study design:** cRCT with 2 intervention arms **Unit of allocation:** clusters (villages) **Number of units:** 26 villages randomized into 2 arms equally. Each cluster consisting of ≥ 500 households

Kafy 2017 *(Continued)*

	Outcome assessment/surveillance type: 60 children randomly selected from each village to participate in the study • Active case detection for malaria episodes was done on the cohort of children aged 0.5–10 years weekly during the peak of the malaria season (September–November) and fortnightly during the remainder of the year, for a total of 30 annual visits. during 12 periods of 6 consecutive days at 6-weekly intervals. Malaria was confirmed by RDT (SD BIOLINE-Malaria Ag P.f/P.v.; Standard Diagnostics, Inc.), or microscopy, or both. • Prevalence of infection was measured once each year, during September to October. Cohort of children were tested for *P falciparum* infection using RDTs (SD BIOLINE-Malaria Ag P.f/P.v.; Standard Diagnostics, Inc.) irrespective of symptoms. **Length of follow-up:** 1 June 2012 to 31 May 2015 **Adjustment for clustering:** yes
Participants	**Number of participants:** total population in study area in 2011 was 139,566. Over the 3-year study period, 7529 children were recruited who were followed up cumulatively for 17,284 person-years. **Population characteristics:** a baseline household census estimated that the area comprised approximately 119,000 households in 197 villages with 600,000 inhabitants who were predominantly dependent on rain-fed agriculture. Mean age of cohort children were similar across all study arms (about 5–6 years old). **Withdrawal and loss to follow-up:** not reported
Interventions	**Comparison: IRS + ITN vs ITN alone** **IRS** Active ingredient, dosage, and formulation: deltamethrin 25 mg/m^2 in 2012 (formulation not reported, Chema Industries), bendiocarb 200 mg/m^2 in 2013 and 2014 (Ficam 80%, wettable powder, Bayer) Frequency of spraying: IRS was conducted in August and late December of each year Coverage: 99% in 2012, 82% in 2013, and 83% in 2014 Buffer size between clusters: minimum 3 km between the edges of adjoining clusters **ITN** Active ingredient and dosage: deltamethrin 55 mg (PermaNet 2.0) Coverage: an annual intervention assessment survey showed that household net ownership was 99.6% in 2012, 82.1% in 2013, and 98.6% in 2014 Compliance: defined as the proportion of affirmative responses to the question "Did this child sleep under an LLIN last night?" In 2012, this was 79% in both arms. In 2013, it was 74% in the LLIN-only arm and 75% in the LLIN + IRS arm. In 2014, it was 82% in both study arms. **Control** ITN only as above **Cointerventions:** none reported
Outcomes	• Incidence of malaria in children aged 6 months to 10 years • Prevalence of malaria infection in children aged 6 months to 10 years • Deltamethrin susceptibility using WHO discriminating dose tests • Prevalence of pyrethroid-resistant 1014F *kdr* allele • Cost and cost-effectiveness

Kafy 2017 *(Continued)*

Location profile	**Study location:** Galabat, south-east Sudan, located around 80 km from Gedarif town and borders Ethiopia **Malaria endemicity:** highly seasonal **EIR:** not reported **Population proximity/density:** not reported ***Plasmodium spp*:***P falciparum* accounts for 95% of the malaria burden
Vector profile	**Primary (and secondary) vector species:***An arabiensis* **Vector behaviour (nature, stability, adult habitat, peak biting times, exophilic/endophilic, exophagic/endophagic, anthropophilic/zoophilic):** not reported **Phenotypic resistance profile:** mean percentage mortality in the LLIN arm (65.0%, 95% CI 44.6% to 85.3%) was not significantly different from that of the LLIN + IRS arm (60%, 95% CI 38.2% to 82.2%) during 2012 (t = 0.425; degrees of freedom 9; P = 0.68). **Genotypic resistance profile:***Vgsc-1014F* allelic frequency was about 60% in mosquitoes sampled from both study arms in 2012. **Method of mosquito collection:***Anopheles* larvae and pupae were collected annually during the rainy season. Adults were collected using pyrethrum spray catches. 24 *An arabiensis* females per cluster were selected at random for *Vgsc-1014F* genotyping to estimate a cluster-specific resistance marker frequency.
Notes	For inclusion in the review meta-analyses, we calculated adjusted risk ratios for prevalence from the reported adjusted odds ratios following the methodology stated in Section 12.5.4.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Clusters were randomly allocated using a restricted randomization computerized procedure. Balance criteria were prevalence of *P falciparum* infection, ITN use, *kdr* frequency in *An arabiensis* and cluster population size. Out of 200,000 random allocations, 8000 yielded balance between study arms on these criteria, from which 1 sequence was randomly selected.
Allocation concealment (selection bias)	Low risk	The 26 clusters in Gedarif, Sudan were randomized to receive LLIN + IRS or LLINs alone, using restricted randomization to ensure balance between study arms. Balance criteria were: prevalence of *P falciparum* infection and ITN use as determined in a baseline survey, kdr frequency in *An arabiensis* from a survey of mosquito collections carried out in each cluster, and cluster population size. Out of 200,000 random allocations of the 26 clusters, 8000 yielded balance between study arms on these criteria. Of these, 1 allocation was randomly chosen, after verifying that the imposed restriction did not introduce undue dependence between clusters.
Blinding of participants and personnel (performance bias) Incidence of malaria	Low risk	Participants and personnel were not blinded to intervention. Low risk of bias for both incidence and prevalence. RDTs and microscopy were used to confirm malaria infection.

Kafy 2017 *(Continued)*

Blinding of participants and personnel (performance bias) Prevalence of malaria	Low risk	Participants and personnel were not blinded to intervention. Low risk of bias for both incidence and prevalence. RDTs and microscopy were used to confirm malaria infection.
Blinding of outcome assessment (detection bias) Incidence of malaria	Low risk	Participants and personnel were not blinded to intervention. Low risk of bias for both incidence and prevalence. RDTs and microscopy were used to confirm malaria infection.
Blinding of outcome assessment (detection bias) Prevalence of malaria	Low risk	Participants and personnel were not blinded to intervention. Low risk of bias for both incidence and prevalence. RDTs and microscopy were used to confirm malaria infection.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No report of withdrawals.
Selective reporting (reporting bias)	Low risk	All children-days were analyzed. The study protocol reported 1 each outcome as stated in the clinical trials register (note: retrospectively registered).
Recruitment bias	Low risk	Cohort of children were randomly selected.
Loss of clusters	Low risk	No clusters were lost.
Baseline imbalance	Low risk	Although baseline information was not available, key effect modifiers such as age and LLIN usage were measured during the study and there were no significant differences.
Incorrect analysis	Low risk	Adjustment for clustering was done.
Comparability with RCTs randomizing participants	Low risk	Because the intervention is expected to have community level impact as well as individual impact, cRCTs are the most appropriate study design to capture this.
Other bias	Low risk	No other biases.

Keating 2011

Study characteristics	
Methods	**Study design:** cRCT with 2 intervention arms **Unit of allocation:** clusters (villages) **Number of units:** 58 randomized villages in each arm **Outcome assessment/surveillance type:** 15 houses within each village were randomly selected to serve as ultimate sampling units, giving 870 houses in each arm of the study. Household residents were given a questionnaire and took a RDT (Carestart) for malaria infection. Positive tests were confirmed by blood smear microscopy. **Length of follow-up:** 3–4 months after spraying (6–15 October 2009) **Adjustment for clustering:** yes
Participants	**Number of participants:** 7273 resided in participating houses. In the paper, 5508 total from Table 2 but 5502 stated in results.

Keating 2011 *(Continued)*

	Population characteristics: the distribution of participants living in houses located in treatment and control villages was similar on sex, age, employment status of the respondent, and education level **Withdrawal and loss to follow-up:** test refusal rates differed between treatment (8.5%) and control (12.7%) arms (P < 0.05)
Interventions	**Comparison: IRS + ITN vs ITN alone** **IRS** Active ingredient and dosage: DDT 1–2 g/m^2 Formulation: wettable powder Frequency of spraying: once, June–July 2009 Coverage: minimum 80% target (84.8% of households sampled sprayed within 12 months) Buffer size between clusters: > 5 km between intervention and control villages. in 2 instances where a treatment village was too close (< 5 km) to a control village, the closest village > 5 km was selected into the control arm. **ITN** Any ITN that was treated at least once in last 11 months, or was an LLIN Coverage: measured as people living in household owning ≥ 1 ITN: 75.8% (range 74.2–77.4%) Compliance: measured as individuals using ITN in the previous night: 50.7% (range 48.6–52.8%) **Control** ITN only as above Coverage: measured as people living in household owning ≥ 1 ITN: 72.0% (range 70.2–73.7%) Compliance: measured as people using ITN in the previous night: 46.2% (range 43.9–48.6%) **Cointerventions:** larval habitat management and continued case management
Outcomes	• Malaria prevalence: parasite infection and febrile illness data from all household residents aged > 1 month requiring a positive RDT (Carestart) and a positive thick blood film
Location profile	**Study location:** Gash Barka, West lowlands of Eritrea, mostly rural and agricultural. Altitudes were 1500–3000 m above sea level. 30% of the country's population lived here. Approximately 200 mm per year precipitation. Temperatures were extremely hot and dry climatic conditions with seasonal precipitation, concentrated in the summer months. **Malaria endemicity:** season with peak transmission occurring September–November. Smaller malaria season March–April **EIR:** study references an estimated annual range of 0–70.6 (Shililu 2004) **Population proximity/density:** not reported ***Plasmodium* spp:***P falciparum* with rare reports of *P vivax*
Vector profile	**Primary (and secondary) vector species:***An arabiensis* and *An gambiae s.s.* **Vector behaviour (nature, stability, adult habitat, peak biting times, exophilic/endophilic, exophagic/endophagic, anthropophilic/zoophilic):** not reported **Phenotypic resistance profile:** not reported **Genotypic resistance profile:** not reported

Keating 2011 *(Continued)*

Method of mosquito collection: no entomological data collected

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Fifty-eight (58) villages within Gash Barka were randomly …" Comment: however, randomization procedure was not described.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) Incidence of malaria	Low risk	Outcome not reported.
Blinding of participants and personnel (performance bias) Prevalence of malaria	Low risk	Participants and personnel were not blinded to the intervention status; however, the outcome would not be affected by this knowledge.
Blinding of outcome assessment (detection bias) Incidence of malaria	Low risk	Outcome not reported.
Blinding of outcome assessment (detection bias) Prevalence of malaria	Low risk	Outcome assessors were not blinded to the intervention status; however, the outcome was measured using an objective tool (Carestart RDT) and would not be affected by this knowledge.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 time point used, not applicable.
Selective reporting (reporting bias)	Low risk	The study only intended to report the relationship between IRS and parasite prevalence and this outcome was provided. Numbers appeared correct, assumed typographical error in table 2, should read 5502.
Recruitment bias	Low risk	Households for survey were randomly selected.
Loss of clusters	Low risk	No mention of lost clusters.
Baseline imbalance	Unclear risk	Baseline data were not displayed but due to randomization this should be accounted for.
Incorrect analysis	Low risk	Adjustment for clustering was done.
Comparability with RCTs randomizing participants	Low risk	Because the intervention is expected to have community level impact as well as individual impact, cRCTs are the most appropriate study design to capture this.
Other bias	Low risk	No other biases.

Loha 2019

Study characteristics	
Methods	**Study design:** 2 × 2 factorial, cluster-randomized, controlled trial. Villages were randomized to 1 of 4 arms: 1. LLIN + IRS; 2. LLIN alone; 3. IRS alone; or 4. control. For this review, the relevant comparison was 1. LLIN + IRS vs 2. LLIN alone. **Unit of allocation:** village **Number of units**: 176 total (44 in each arm) **Outcome assessment/surveillance type:** active and passive case detection. Through weekly household visits, study participants with a fever or history of fever were encouraged to present to the nearest health posts for testing and treatment. Health centres were regularly visited to find malaria cases not reported to field workers. **Length of follow-up:** 2.5 years (121 weeks) **Adjustment:** the incidence of malaria was calculated using methods for cluster randomized trials that take into account the intracluster correlation coefficient.
Participants	**Number of participants:** 9068 in IRS and ITNs arm, 8521 in LLIN-only arm – approximately 196 per cluster **Population characteristics:** predominantly rural. Residents primarily depend on farming, livestock rearing, and to a lesser extent, fishing **Inclusion criteria for participants:** all consenting residents of households in all clusters were recruited for the study.
Interventions	**IRS** Active ingredient and dosage: propoxur: 2 g/m^2 Formulation: WP Frequency of spraying: annually Time of spraying: prior to transmission season (September 2014, July 2015, July 2016) Spraying conducted by: locally recruited spray personnel and supervisors. Coverage: 95–96% **LLIN** Active ingredient and dosage: deltamethrin 55 mg/m^2 (SD 25%) Time of implementation: at the beginning of study, all households in the IRS + LLIN and LLIN-alone arms received new LLINs free of charge (procured June 2014, first follow-up October 2014). 1 net was given for a family of 1–2 people, 2 nets for a family of 3–5 people, 3 nets for a family of 6–7 people, and 4 nets for a family of ≥ 8 people Formulation: PermaNet 2.0 Coverage and compliance both decreased significantly during the study period. Coverage measure: household ownership of ≥ 1 LLIN Coverage in IRS arm: 100% (at baseline) Coverage in control arm: 100% (at baseline) Coverage after 110 weeks (both arms): 8%

Loha 2019 *(Continued)*

	Compliance measure: whether any household members used an LLIN the night before the day of the interview Compliance: in IRS arm: 47% (weeks 1–26), 26% (weeks 26–53), 8% (weeks 53–79), 1% (weeks 79–121) Compliance in control arm: 49% (weeks 1–26), 27% (weeks 26–53), 6% (weeks 53–79), 1% (weeks 79–121) **Cointerventions:** none described
Outcomes	• Malaria case incidence in all ages (determined by the detection of *P falciparum* or *P vivax* by RDTs in participants with a fever or history of fever within the previous 48 hours upon arrival to health posts) • Malaria prevalence in all age groups at week 57 • Anaemia prevalence (Hb < 11 g/dL) in children aged 6–59 months
Location profile	**Study location:** Ethiopia (Adami Tullu, Adami Tullu-Jiddo-Kombolcha district, East Shewa Zone, Oromia Regional State) **Malaria endemicity:** seasonal, with the peak malaria transmission season from September to December ***Plasmodium* species:** *P falciparum* and *P vivax*
Vector profile	**Primary (and secondary) vector species**: *An arabiensis* (primary), *An pharoensis* (auxiliary) **Phenotypic resistance profile:***An arabiensis* was susceptible to propoxur (a carbamate), but resistant to the pyrethroid insecticides. *An pharoensis* was susceptible to all pyrethroids and carbamates tested **Method of mosquito collection:** malaria vectors were collected in randomly selected houses using light trap catches (LTC), pyrethrum spray catches (PSC), and artificial outdoor pit shelters (PIT). LTC and PIT were placed in 1 house per cluster. PSC was performed in 4 houses per cluster. LTC, PSC, and PIT were used to monitor the impact of the interventions on *An arabiensis* host-seeking density, indoor resting density, and outdoor resting density, respectively. In addition, human landing catch was performed indoors and outdoors in 1 house in 1 cluster per study arm to monitor the impact the interventions on *An arabiensis* human biting rates.
Notes	**Intracluster correlation coefficient:** 0.01 (obtained from study authors. This was used to calculate an adjusted Incidence RR by review authors).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random sequence was computer generated.
Allocation concealment (selection bias)	Low risk	Randomization was carried out in Bergen, Norway, to prevent selection bias by concealing the allocation sequence from the field researchers assigning villages to intervention groups.
Blinding of participants and personnel (performance bias) Incidence of malaria	Low risk	Participants and personnel were not blinded to intervention. Low risk of bias for both incidence and prevalence because the outcomes measured were objective.
Blinding of participants and personnel (performance bias) Prevalence of malaria	Low risk	Participants and personnel were not blinded to intervention. Low risk of bias for both incidence and prevalence because the outcomes measured were objective.

Loha 2019 *(Continued)*

Blinding of outcome assessment (detection bias) Incidence of malaria	Low risk	Participants and personnel were not blinded to intervention. Low risk of bias for both incidence and prevalence because the outcomes measured were objective.
Blinding of outcome assessment (detection bias) Prevalence of malaria	Low risk	Participants and personnel were not blinded to intervention. Low risk of bias for both incidence and prevalence because the outcomes measured were objective.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Proportion lost to follow-up in each intervention arm was not described. The authors did state that in order to minimize any loss to follow-up, all residents were followed and recorded if they moved out of the trial area or moved from 1 cluster to another cluster with a different intervention.
Selective reporting (reporting bias)	Low risk	All outcomes described in the protocol were reported, with the exception of EIR, which could not be calculated as none of the collected mosquitoes were found to be infected.
Recruitment bias	Low risk	All consenting residents of households in all clusters were recruited for the study.
Loss of clusters	Low risk	No loss of clusters.
Baseline imbalance	Low risk	Study groups were comparable, except for house design.
Incorrect analysis	Low risk	No evidence of incorrect analyses conducted.
Comparability with RCTs randomizing participants	Low risk	Comparable.
Other bias	Low risk	No other risks identified.

Namuganga 2021

Study characteristics	
Methods	**Study design:** interrupted time series to observe the impact of the implementation and sustained use of IRS **Unit of allocation:** N/A **Outcome assessment/surveillance type:** passive surveillance of malaria cases using health system data in 5 study areas. Entomological surveys were conducted in households in the single study area of Nagongera. **Length of follow-up:** 12 months before intervention, 59 months after intervention **Adjustment:** mixed effects negative binomial regression models with random intercepts were created for each health facility. Coefficients for the exposure variable were exponentiated to represent the incidence rate ratio (IRR) comparing the incidence of malaria in the month of interest relative to the baseline period. The models adjusted for time-varying variables that impact malaria burden and malaria case detection at the health facility. These variables included monthly rainfall at the health facility lagged by 1 month extracted from the Climate Hazards Infrared Precipitation with Stations database, indicator variables for month of the year (to adjust for seasonal effects), the proportion of tests that were RDTs in that month (vs microscopy), and the number of individuals who attended the health facility but were not suspected of having malaria in that month (to adjust for potential changes in care-seeking behaviours over time).

Namuganga 2021 *(Continued)*

Participants	**Number of participants:** not described **Population characteristics:** not described **Inclusion criteria for participants:** all participants resident in the 5 study areas
Interventions	**IRS** Active ingredient and dosage: bendiocarb up to 2016. Actellic 300CS from 2016 until the end of study Frequency of spraying: 6-monthly (bendiocarb). Actellic was implemented annually. Time of spraying: December 2014 to February 2015; June–July 2015; November–December 2015. Annual spraying times after this were not described. Coverage: 96.9% in Nagongera region. Other areas not described Compliance: Not reported Buffer size between clusters: N/A **LLIN** Active ingredient and dosage: Not reported Time of implementation: ULLIN distribution took place in 2013–2014. This was repeated in 2017–2018. All study areas received conventional LLINs – rather than pyrethroid-PBO nets which were distributed in other areas of the country – due to concerns of antagonism between pyrethroid-PBO nets and Actellic 300CS. Formulation: Not reported Coverage: in Nagongera region (other areas not described): • 2013: 71.0% (proportion of households with ≥ 1 LLIN); 22.5% (proportion of households with ≥ 1 LLIN per 2 people) • 2015: 95.5% (proportion of households with ≥ 1 LLIN); 62.0% (proportion of households with ≥ 1 LLIN per 2 people) Compliance: Not reported
Outcomes	• Malaria incidence: mean monthly confirmed cases of malaria (adjusted for testing rate) • Human biting rate (number of female *Anopheles* mosquitoes captured per house-night of collection)
Location profile	**Study location:** 5 Malaria Reference Centres in Eastern Uganda: Nagongera (Tororo district); Amolatar (Amolatar); Dokolo (Dokolo); Orum (Otuke), and Alebtong (Alebtong) **Malaria endemicity:** high, perennial with 2 annual peaks following the rainy season
Vector profile	**Primary (and secondary) vector species:***An gambiae* and *An arabiensis* **Phenotypic resistance profile (Nagongera):** • *An gambiae*: deltamethrin/pyrethrin (20–40% mortality). Bendiocarb (> 80% mortality) • *An arabiensis:* deltamethrin/pyrethrin (60–80% mortality). Bendiocarb (100% mortality) **Method of mosquito collection:** entomological surveys conducted in households enrolled in cohort study, using CDC light traps, deployed from 7 pm to 7 am.
Notes	

Risk of bias

Namuganga 2021 *(Continued)*

Bias	Authors' judgement	Support for judgement
Blinding of participants and personnel (performance bias) Incidence of malaria	Low risk	It would not have been possible to prevent knowledge of the interventions, but this is thought unlikely to have influenced any of the reported outcomes.
Blinding of participants and personnel (performance bias) Prevalence of malaria	Low risk	It would not have been possible to prevent knowledge of the interventions, but this is thought unlikely to have influenced any of the reported outcomes.
Blinding of outcome assessment (detection bias) Incidence of malaria	Low risk	It would not have been possible to prevent knowledge of the interventions, but this is thought unlikely to have influenced any of the reported outcomes.
Blinding of outcome assessment (detection bias) Prevalence of malaria	Low risk	It would not have been possible to prevent knowledge of the interventions, but this is thought unlikely to have influenced any of the reported outcomes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data likely to bias the results.
Selective reporting (reporting bias)	Low risk	All primary outcomes were reported.
Intervention independent of other changes	Low risk	No other changes implemented during the study period.
Shape of the intervention effect prespecified	Low risk	The point of analysis is the point of the intervention.
Intervention unlikely to affect data collection	Low risk	The methods of data collection were the same before and after the intervention.
Other bias	Low risk	No other biases detected.

Pinder 2015

Study characteristics	
Methods	**Study design:** cRCT with 2 intervention arms **Unit of allocation:** clusters of villages, each cluster consisted of 1–3 neighbouring villages (97 villages in total) **Number of units:** 35 randomized clusters in each arm. A subset of 16 clusters per arm was used for entomological assessment. **Outcome assessment/surveillance type** • Children in the study villages aged 6 months to 14 years were sampled according to cluster size and enrolled into a study cohort. • Incidence rates monitored through passive case detection at local health facilities • Prevalence and parasite rates were measured at the end of each transmission season

Pinder 2015 *(Continued)*

	• Mosquito density was assessed using light traps and exit traps in 6 sentinel sites in each of 32 clusters, 1 night per month **Length of follow-up:** 2 years (2010–2011), 2 transmission seasons (June–December 2010 and 2011) **Adjustment for clustering:** cluster-adjusted measures were presented for some outcomes.
Participants	**Number of participants:** control: 3949 enrolled children, intervention: 3896 **Population characteristics:** cohort of children aged < 14 years. Ethnic origin varied with more Mandinka and lower Fula people in the LLIN arm than in the IRS + LLIN arm. **Withdrawal and loss to follow-up:** separate analysis was done per survey, each time a survey was done, cohorts would be replenished.
Interventions	**Comparison: IRS + ITN vs ITN alone** **IRS** Active ingredient and dosage: DDT target dose 2 g/m^2 (2010 mean: 1.69 g/m^2, 2011: 3.27 g/m^2) Formulation: 75% WP Frequency of spraying: once per transmission season (15–28 July 2010, and 20 July to 9 August 2011) Coverage: per cluster in 2010: 86% (range 82.84–90.16%); per cluster in 2011: 83% (range 79.27–86.28%) Buffer size between clusters: > 2 km **ITN** Active ingredient and dosage: permethrin 2% w/w (Olyset Net) Coverage: nets were provided to cover all sleeping spaces as determined by a baseline survey. 59% coverage in June 2010. 89% coverage in January 2011. 93% in January 2012. Compliance: not reported **Control** ITN only as above Coverage: 2010: 62%; 2011: 92%; 2012: 96% Compliance: not reported Cointerventions: none reported
Outcomes	**Primary outcomes** • Incidence of clinical malaria assessed by passive case detection • Number of *An gambiae s.l.* collected per light trap per night **Secondary outcomes** • Hb concentration • Proportion of children with moderate anaemia (< 80 g/L) and severe anaemia (< 50 g/L) • Presence of malaria parasites • Parasite density • Proportion of children with high parasitaemia (> 5000 parasites/µL) • Prevalence of children with enlarged spleens measured at the end of the transmission season each year • Sporozoite rate estimates in trapped mosquitoes

Pinder 2015 *(Continued)*

- Estimated EIR (mean number of infective mosquito bites per person per season)

Location profile	**Study location:** Upper River Region of The Gambia, > 110 children aged 6 months to 14 years on 1 June 2010 **Malaria endemicity:** moderate seasonal malaria transmission **EIR:** estimated seasonal mean from the control arm of the study measured 2.44 (range 0.69–6.39) in the first year and 0.29 (0.003–2.66) in the second year **Population proximity/density:** not reported ***Plasmodium*spp:***P falciparum*
Vector profile	**Primary (and secondary) vector species:***An gambiae s.l.* **Vector behaviour (nature, stability, adult habitat, peak biting times, exophilic/endophilic, exophagic/endophagic, anthropophilic/zoophilic):** not reported **Phenotypic resistance profile:** not reported **Genotypic resistance profile:** not reported **Method of mosquito collection:** light and exit traps indoors in 6 rooms in 6 different randomly selected compounds per cluster, 1 night per month
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Villages were randomly assigned using a computerized algorithm.
Allocation concealment (selection bias)	Low risk	Villages were randomly assigned using a computerized algorithm.
Blinding of participants and personnel (performance bias) Incidence of malaria	Low risk	Participants and personnel were not blinded to intervention.
Blinding of participants and personnel (performance bias) Prevalence of malaria	Low risk	For prevalence, risk of bias was low as every participant had their blood taken.
Blinding of outcome assessment (detection bias) Incidence of malaria	Unclear risk	Unclear risk of bias for incidence due to self-reporting of sickness before confirmation by microscopy, an objective assessment.
Blinding of outcome assessment (detection bias) Prevalence of malaria	Low risk	For prevalence, risk of bias was low as every participant had their blood taken. Observer bias was reduced where feasible. Slide microscopists and their supervisors were blinded to the identity and intervention status of the participants.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Incomplete outcome data were minimal and similar between intervention arms. Attrition between 2010 and 2011 accounted for by topping up cohort with newborn children (312 in LLIN + IRS arm; 324 in LLIN-only arm).

Pinder 2015 *(Continued)*

Selective reporting (reporting bias)	Low risk	The study protocol reported on each outcome as stated in the clinical trials register (note: retrospectively registered).
Recruitment bias	Low risk	Cohort of children were randomly selected from household survey lists using statistical software.
Loss of clusters	Low risk	No clusters were lost.
Baseline imbalance	Low risk	Baseline data were displayed and similar.
Incorrect analysis	Low risk	Adjustment for clustering was done.
Comparability with RCTs randomizing participants	Low risk	Because the intervention was expected to have community level impact as well as individual impact, cRCTs are the most appropriate study design to capture this.
Other bias	Low risk	No other biases.

Protopopoff 2018

Study characteristics	
Methods	**Study design:** cRCT with 4 intervention arms using a 2 × 2 factorial design • arm 1: standard LLIN (Olyset Net) • arm 2: standard LLIN (Olyset Net) + IRS • arm 3: pyrethroid net + synergist PBO (Olyset Plus) • arm 4: pyrethroid net + synergist PBO (Olyset Plus) + IRS **Therefore, there were 2 comparisons for this review: arm 1 vs arm 2, and arm 3 vs arm 4** **Unit of allocation:** clusters comprised from 40 villages **Number of units:** 48 clusters randomized into 4 arms equally **Outcome assessment/surveillance type:** cross-sectional surveys of children aged 6 months to 14 years were done to determine the prevalence of *Plasmodium* spp infection. The main endpoint for assessment of the IRS was 9 months postintervention. Up to 3 children from 55 households with eligible participants per cluster were randomly selected for each survey. **Length of follow-up:** originally planned for 18 months (1 January 2015 to 30 June 2016) but was subsequently extended to 24 months (1 January 2014 to 31 December 2016) **Adjustment for clustering:** yes
Participants	**Number of participants:** at the primary endpoint for assessment of the IRS, the numbers of children recruited were 933 in arm 1, 877 in arm 2, 883 in arm 3, and 969 in arm 4 **Population characteristics:** • total population in core and buffer areas ranged from 31,138 to 38,081 • total population in the core area of the clusters between 14,845 and 16,358 **Withdrawal and loss to follow-up:** a fresh cohort was recruited for each cross-sectional survey and ITT analysis was conducted.
Interventions	**IRS**

Protopopoff 2018 *(Continued)*

	Active ingredient and dosage: pirimiphos-methyl at the recommended dosage 1 g/m^2 Formulation: 30% capsule suspension (Actellic 300CS) Frequency of spraying: once in February 2015 Coverage: per cluster: 94% (95% CI 92% to 96%) in arm 2 and 94% (95% CI 87% to 97%) in arm 4 Buffer size between clusters: minimum outer buffer zone of 300 m. Only the inner core area was used for the measurement of study outcomes **ITN** Active ingredient and dosage: permethrin 2% w/w (Olyset Net) and permethrin 2% (Olyset Plus) and PBO 1% w/w Coverage: 9 months postintervention, coverage defined as household owning ≥ 1 LLIN (study LLIN or any other LLIN) was 98% (95% CI 96% to 99%) in arm 2 and 98% (95% CI 95% to 99%) in arm 4 Compliance: at 9 months postintervention, compliance defined as residents declaring to use an LLIN the previous night (study LLIN or any other LLIN) was 76% (95% CI 70% to 80%) in arm 2 and 77% (95% CI 70% to 83%) in arm 4 **Control** ITN only as above Coverage: at 9 months postintervention, coverage defined as household owning ≥ 1 LLIN (study LLIN or any other LLIN) was 97% (95% CI 93% to 99%) in arm 1 and 98% (95% CI 97% to 99%) in arm 3 Compliance: at 9 months postintervention, compliance defined as residents declaring to use a LLIN the previous night (study LLIN or any other LLIN) was 80% (95% CI 75% to 85%) in arm 1 and 78% (95% CI 73% to 82%) in arm 3 **Cointerventions:** none reported
Outcomes	• Prevalence of *Plasmodium* spp infection • Proportion of children with moderate-to-severe anaemia (defined as Hb < 8 g/dL) • EIR defined as the mean number of infective mosquito bites per household per month • Adult mosquito density per night per household
Location profile	**Study location:** Northwest Tanzania, Muleba Distract, Kagera Region, the study area comprised 29,365 households and 135,900 people **Malaria endemicity:** perennial with peaks after the rainy season. Rainfall occurs in 2 seasons: the "short rains" in October–December (mean monthly rainfall 160 mm) and the "long rains" in March–May (mean monthly rainfall 300 mm) **EIR:** not measured at baseline **Population proximity/density:** not reported ***Plasmodium* spp:***P falciparum*
Vector profile	**Primary (and secondary) vector species:***An gambiaes.s.* (*An arabiensis* and *An funestus*) **Vector behaviour (nature, stability, adult habitat, peak biting times, exophilic/endophilic, exophagic/endophagic, anthropophilic/zoophilic):** not reported **Phenotypic resistance profile:***An gambiae s.l.* had high levels of resistance to pyrethroids. **Genotypic resistance profile:** the *Vgsc* gene mutation was found in all tested *An gambiae s.l.* with co-occurrence of *Vgsc-1014F* and *Vgsc-1014S* in 22 (9%) of 234 *An gambiae s.l.* mosquitoes. No mutation was found in the 247 *An arabiensis* tested.

Protopopoff 2018 *(Continued)*

	Method of mosquito collection: mosquito surveillance was done from March 2015 to December 2016, in each cluster by a project field assistant for 1 night per month in 7 randomly selected houses per cluster using CDC Miniature Light Trap Model 512 (John W Hock Company, USA).
Notes	For inclusion in the review meta-analyses, we calculated adjusted risk ratios for prevalence from the reported adjusted odds ratios following the methodology stated in Section 12.5.4.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	During each survey, we randomly sampled 55 households with children aged 6 months to 14 years from the core area of each cluster using the census lists.
Allocation concealment (selection bias)	Low risk	The inhabitants of each cluster to the type of LLINs received. The 2 types of nets were of similar colour and shape, and only distinguishable by label codes and coloured thread inserted during manufacture. Additionally, field staff who took blood samples in the cross-sectional surveys were blinded to the study arms the clusters were assigned to. It was not possible to blind either the investigators or the participants to the treatment allocation of IRS but we do not feel this would impact the outcome.
Blinding of participants and personnel (performance bias) Incidence of malaria	Low risk	This outcome was not measured.
Blinding of participants and personnel (performance bias) Prevalence of malaria	Low risk	Field staff who took blood samples in the cross-sectional surveys were blinded to the study arms the clusters were assigned to. It was not possible to blind either the investigators who assessed the blood samples or the participants to the treatment allocation of IRS but we do not consider this would impact the outcome which was assessed by RDT (an objective test).
Blinding of outcome assessment (detection bias) Incidence of malaria	Low risk	This outcome was not measured.
Blinding of outcome assessment (detection bias) Prevalence of malaria	Low risk	Field staff who took blood samples in the cross-sectional surveys were blinded to the study arms the clusters were assigned to. It was not possible to blind either the investigators or the participants to the treatment allocation of IRS but we do not consider this would impact the outcome which was assessed by RDT (an objective test).
Incomplete outcome data (attrition bias) All outcomes	Low risk	A new cohort of children was used for each cross-sectional survey.
Selective reporting (reporting bias)	Low risk	The study protocol reported each outcome as stated in the clinical trials register (note: retrospectively registered).
Recruitment bias	Low risk	Households were randomly selected from census lists.
Loss of clusters	Low risk	No clusters were lost.

Protopopoff 2018 *(Continued)*

Baseline imbalance	Low risk	Baseline data was displayed. No significant differences at baseline for outcomes the study assessed.
Incorrect analysis	Low risk	Adjustment for clustering was done.
Comparability with RCTs randomizing participants	Low risk	Because the intervention is expected to have community level impact as well as individual impact, cRCTs are the most appropriate study design to capture this.
Other bias	Low risk	No other biases.

West 2014

Study characteristics	
Methods	**Study design:** cRCT with 2 intervention arms **Unit of allocation:** clusters (villages) **Number of units:** 25 randomized villages in each arm. A subset of 20 villages per arm was used for entomological assessment. **Outcome assessment/surveillance type:** see below in 'Outcomes' section **Length of follow-up:** 3 postintervention cross-sectional household surveys were undertaken in 2012. Survey A (23 February to 31 March) was after the short rainy season and 2 months after the first spray round. Survey B (25 June to 31 July) was after the long rainy season, 6 months after the first spray round, and 2 months after the second spray round. Survey C (25 October to 4 December) was 6 months after the second spray round and 10 months after the first. Baseline surveys were conducted in 2011 during the same periods as surveys A and B. **Adjustment for clustering:** yes
Participants	**Number of participants:** for each of the surveys, a different number of participants were used in each cohort • Survey A: 2192 children in control arm, 2348 in intervention arm • Survey B: 2045 children in control arm, 2207 in intervention arm • Survey C: 2101 children in control arm, 2303 in intervention arm **Population characteristics:** cohort of children aged 6 months to 14 years, villages had to be sprayed with IRS in the baseline year. **Withdrawal and loss to follow-up:** 82.2–84.4% of intervention participants tested in each survey. 78.3–80.8% of control participants tested
Interventions	**IRS** Active ingredient and dosage: bendiocarb 400 mg/m^2 Formulation: 80% WP Frequency of spraying: 2 rounds of spraying (December 2011 to January 2012) and (April 2012 to May 2012), timed to precede the peak in malaria cases that normally occurs at the end of each rainy season. Coverage: survey A: 92.1% (95% CI 88.4% to 94.7%) (1215); survey B: 89.5% (95% CI 84.0% to 93.2%) (1138); survey C: 89.3% (95% CI 83.6% to 93.2%) (1209)

West 2014 *(Continued)*

	Buffer size between clusters: each village was divided into a core surveillance area consisting of ≥ 200 houses and approximately 1 km radius, where the surveys were conducted, and an outer buffer zone of approximately 1 km width which also received treatment but in which there was no outcome monitoring. **ITN** Active ingredient and dosage: permethrin 2% w/w (Olyset Net) Coverage measured as % of households with ≥ 1 ITN per sleeping space: survey A: 57.2 (range 53.6–60.7) (1215); survey B: 57.4 (range 54.0–60.9) (1142); survey C: 56.8 (range 51.7–61.8) (1211) Coverage measured as % of households with ≥ 1 ITN: survey A: 89.0 (range 87.1–90.6) (1216); survey B: 88.2 (range 85.7–90.3) (1142); survey C: 83.8 (range 79.9–87.1) (1211) Compliance measured as % of study children that reported sleeping under an ITN the night previous to the survey: survey A: 53.0 (range 47.5–58.3) (2349); survey B: 44.1 (range 39.2–49.2) (2207); survey C: 36.1 (range 31.0–41.5) (2303) **Control** ITN only as above Coverage measured as % of households with ≥ 1 ITN per sleeping space: survey A: 52.2 (range 47.8–56.5) (1178); survey B: 51.6 (range 47.0–56.0) (1094); survey C: 52.8 (range 47.6–58.0) (1168) Coverage measured as % of households with ≥ 1 ITN: survey A: 85.8 (range 83.7–87.7) (1177); survey B: 82.5 (range 78.7–85.7) (1096); survey C: 78.2 (range 74.3–81.6) (1170) Compliance measured as % of study children that reported sleeping under an ITN the night previous to the survey: survey A: 46.6 (range 41.7–51.6) (2193); survey B: 40.7 (range 34.7–47.0) (2045); survey C: 36.0 (range 29.8–42.6) (2101) **Cointerventions:** none reported
Outcomes	• *P falciparum* parasite rate in children aged 6 months to 14 years, 80 households in each cluster. Up to 3 children per household selected. Aimed for a mean of 80 children per cluster. Tested with RDT (Carestart (Pan) Malaria, DiaSys) • Anaemia in children aged < 5 years • Mean Hb in children aged < 5 years. Tested with HemoCue Hb 201+ (Aktiebolaget Leo Diagnostics) • EIR: 20/25 clusters per arm were monitored for 1 night each month from April 2011 to December 2012. 8 randomly selected houses in each cluster • Sporozoite rate
Location profile	**Study location:** north-west Tanzania, Muleba Distract, Kagera Region, the study area included 68,108 households at an altitude of 1100–1600 m above sea level. Rainfall occurred in 2 seasons: the 'short rains' in October–December (mean monthly rainfall 160 mm) and the 'long rains' in March–May (mean monthly rainfall 300 mm). **Malaria endemicity:** perennial with peaks after the rainy season **EIR:** baseline characteristics measured by the study reported a mean per month in the control arm of 1.1 (range 0.4–2.8) and 1.3 (range 0.4–4.4) in the intervention arm **Population proximity/density:** not reported ***Plasmodium* spp:***P falciparum*
Vector profile	**Primary (and secondary) vector species:***An gambiae s.s.* and *An arabiensis* **Vector behaviour (nature, stability, adult habitat, peak biting times, exophilic/endophilic, exophagic/endophagic, anthropophilic/zoophilic):** not reported

West 2014 *(Continued)*

	Phenotypic resistance profile: resistance to pyrethroids in *An gambiae s.s.* **Genotypic resistance profile:** not reported **Method of mosquito collection:** CDC light traps indoors
Notes	For inclusion in the review meta-analyses, we calculated adjusted risk ratios for prevalence from the reported adjusted odds ratios following the methodology stated in Section 12.5.4.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Twenty-five clusters were randomly allocated to receive IRS …" Comment: 200,000 random allocations were generated. 1 allocation was randomly selected from the list of these with no intracluster dependence on key variables.
Allocation concealment (selection bias)	Low risk	Allocation concealment was at low risk of bias considering the computer-randomized allocation.
Blinding of participants and personnel (performance bias) Incidence of malaria	Low risk	Outcome not reported.
Blinding of participants and personnel (performance bias) Prevalence of malaria	Low risk	Participants could not be blinded to the control and intervention. However, the outcomes recorded were objective and at low risk of being affected by intervention arm knowledge.
Blinding of outcome assessment (detection bias) Incidence of malaria	Low risk	Outcome not reported.
Blinding of outcome assessment (detection bias) Prevalence of malaria	Low risk	Outcome assessors were not blinded to the control and intervention. However, the outcomes recorded were objective measurements (using RDTs, and standardized mosquito traps).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention to treat was done, balanced numbers in both arms.
Selective reporting (reporting bias)	Low risk	Outcomes reported matched those in the registered protocol, but children aged 6 months to 10 years rather than 14 years was reported in the trial protocol.
Recruitment bias	Low risk	Cohort of children were randomly selected.
Loss of clusters	Low risk	1 cluster was assigned the wrong intervention and then dropped. Sensitivity analysis was done to show this did not impact the outcome.
Baseline imbalance	Low risk	Baseline characteristics were presented for both study arms and showed similarity across key characteristics.
Incorrect analysis	Low risk	Adjustment for clustering was done.

West 2014 *(Continued)*

Comparability with RCTs randomizing participants	Low risk	Because the intervention is expected to have community level impact as well as individual impact, cRCTs are the most appropriate study design to capture this.
Other bias	Low risk	No other biases.

Anopheles arabiensis: *An arabiensis*; *An funestus*: *Anopheles funestus*; *An gambiae*: *Anopheles gambiae*; cRCT: cluster randomized controlled trial; CSP: circumsporozoite protein; CTPS: carbamate-treated plastic sheeting; DDT: dichloro-diphenyl-trichlorethane; EIR: entomological inoculation rate; ELISA: enzyme-linked immunosorbent assay; IRD-CREC: Institut de Recherche pour le Développement Centre de Recherches Entomologiques de Cotonou; IRS: indoor residual spraying; ITN: insecticide-treated net; ITT: intention to treat; LLIN: long-lasting insecticidal net; *P falciparum*: *Plasmodium falciparum*; *P vivax*: *Plasmodium vivax*; RCT: randomized controlled trial; RDT: rapid diagnostic test; TLLIN: targeted long-lasting insecticidal nets; ULLIN: universal long-lasting insecticidal nets; WHO: World Health Organization; WP: wettable powder.

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

Study	Reason for exclusion
Argyropoulos 2021	The study did not meet the criteria for study design. There was no contemporaneous comparator group, and the study had only 2 time points (pre- and postintervention).
Brutus 2001	The study did not meet the inclusion criteria for intervention as the authors implemented IRS only. No nets were distributed.
Charlwood 2001	The study did not meet the inclusion criteria for intervention. ITNs were not in use. The study evaluated IRS only.
Cot 2001	The study did not meet the intervention criteria, as it compared the impact of different IRS insecticides but there were no ITNs in the study arms.
CTRI/2017/11/010367	The study did not meet the inclusion criteria for intervention. Though the trial was originally planned and designed to include the use of IRS and ITNs in the trial, due to the government's non-clearance, the IRS component was dropped from the project and the trial was carried out and completed with ITNs only.
Galatas 2020	The study did not meet the inclusion criteria for intervention. This was a controlled before-after study. However, both IRS and MDA were distributed in the intervention areas at the same time and, therefore, the IRS is not implemented independently from other changes.
Gari 2016	Study design did not meet inclusion criteria. There were no intervention and control arms to compare. Instead, the study utilized regression analyses to identify risk factors for malaria.
Gimnig 2016	Study design did not meet inclusion criteria. Impact on malaria transmission was observed following the introduction of IRS. However, there was no control group, and the study could not be included as a time series study as it only had 1 pre-intervention survey.
Gunasekaran 2005	The study did not meet the inclusion criteria for intervention as the authors implemented IRS only. No nets were distributed.
Hamel 2011	Study design did not meet inclusion criteria.

Study	Reason for exclusion
	The study was a non-randomized prospective cohort study, comparing transmission of *Plasmodium falciparum* parasitaemia in Rachuonyo District (which received an IRS programme) with Nyando District, an adjacent district with similar malaria transmission levels where IRS was not conducted.
Hsiang 2020	The study did not meet criteria for control. This is a 2 × 2 factorial design evaluating the impact of reactive focal vector control (RVAC) (i.e. IRS in specific communities in response to case detection) and other interventions including reactive focal MDA and reactive case management. All the communities, including those that were not receiving reactive focal IRS, received blanket coverage IRS at the start of the transmission season. Therefore, there is no comparison arm that did not receive IRS.
Keating 2021	The study did not meet the criteria for study design. There is no contemporaneous control. Treatment areas were selected based on prevalence in the previous survey and changed each year. Furthermore, the study did not meet the criteria for interrupted time series as there were not enough time points prior to the intervention.
MacDonald 2018	The study did not meet the criteria for study design.
Matthews 2009	Study design did not meet the inclusion criteria. Controlled before-after study with only 1 village in each of 3 study arms (1 village receiving IRS + ITN, 1 receiving ITN only, 1 control).
NCT02556242	This is a registered trial that will not meet the inclusion criteria as it does not have an appropriate control group. There are 2 study arms. The intervention arm of the trial will receive IRS delivery through targeted reactive spraying in the neighbourhood of recent local cases only; the reference (control) arm of the trial will receive IRS through generalized annual spraying of all structures as per standard current practice.
Protopopoff 2008	Study design did not meet inclusion criteria. The intervention and control areas were not comparable as the intervention areas were densely populated valleys with rice fields while control areas were smaller and less populated. Time series analysis was not possible as there was only 1 baseline measurement prior to intervention.
Rowland 2000	Study did not meet inclusion criteria for intervention, as only IRS was implemented. The study area did not have high coverage of ITNs.
Sharma 2012	The study did not meet the inclusion criteria for intervention, because ITNs were utilized in the unsprayed control area only, not in IRS areas.
Wagman 2020	The study design did not meet the inclusion criteria. This is a complex retrospective observational time series analysis describing the impact of implementing and withdrawing IRS activities across the Segou and Mopti regions in Mali. Study areas were not randomized into IRS or control arms. 2 records reported malaria outcomes in the Segou region, comparing districts that were receiving IRS with those that were not. However, no baseline measurements prior to the introduction of IRS were reported and the study, therefore, did not meet inclusion criteria for interrupted time series or controlled before-after studies. The third record describes the impact of introducing IRS in the Mopti region. The change in malaria transmission is compared to districts that did not receive IRS in Mopti and Segou. However, though there are many villages in the sprayed and unsprayed areas, there was only 1 cluster per arm.

Study	Reason for exclusion
Yadav 2003	The study did not meet the inclusion criteria for intervention. ITNs were not in use. The study evaluated IRS only.
Zhou 2010	Study did not meet inclusion criteria for intervention. This is a time series design following the implementation of IRS. However, ITNs were not distributed until after the study was completed. Household net ownership at the time of the trial was 13%.

IRS: indoor residual spraying; ITN: insecticide-treated net; MDA: mass drug administration.

Characteristics of studies awaiting classification *[ordered by study ID]*

Hamainza 2016

Methods	**Study design:** cluster stepped-wedge design RCT, the study assessed the impact of 4 different IRS insecticide formulations. **Study status:** completed **Unit of allocation:** village or groups of villages **Number of units:** 14 units with mixed interventions **Outcome assessment/surveillance type** • Active monthly parasitological surveys in participating households. Participants were encouraged to seek care through passively offered diagnosis and treatment services in-between surveys. Parasitaemia confirmed with RDT (ICT Malaria *P.f.* cassette test). • Entomological observations were made in 15 households in each cluster. Additionally, human landing catches were conducted both indoors and outdoor. **Length of follow-up:** 29 months in Luangwa and 26 months in Nyimba, starting from January **Adjustment for clustering:** yes
Participants	**Number of participants:** 25,354 at start of study stated in population characteristics; however, figure 2 of the publication suggested 84,275. **Population characteristics:** of these participants, 29% (7412) were children aged < 5 years. The overall cluster populations ranged from 1158 to 3429. **Withdrawal and loss to follow-up:** Figure 2 in the paper suggested many participants withdrew, no ITT analysis stated.
Interventions	**IRS** Active ingredient, dosage, formulation, and coverage: • deltamethrin, wettable granule formulation, 82% • lambdacyhalothrin, capsule suspension, 61% • pirimiphos methyl, emulsifiable concentrate, 53% • pirimiphos methyl, capsule suspension, 69% Frequency of spraying: • October 2010: deltamethrin (clusters 4, 5, 6, and 7). Control (1, 2, 3, 8, 9, 10, 11, 12, 13, and 14) • October 2011: pirimiphos EC (2, 4, 5, 9, 11, and 13); lambdacyhalothrin (6, 7). Control (1, 3, 8, 10, and 12) • November 2012: pirimiphos CS (8, 9, 10, 12, and 14); February 2013: pirimiphos EC (2, 4, and 5); Lambdacyhalothrin (6 and 7). Control (1, 2, 3, 11, and 13)

Hamainza 2016 *(Continued)*

	Coverage: in the first 1–6 months' after IRS implementation (range 0–100%; mean 29.4%) Buffer size between clusters: not reported **ITN** No mass distribution took place as part of the study; however, ITN use was already high (LLIN use in the first 1–6 months' after IRS implementation across all clusters in both arms (range 6.6–100%, mean 68.2%)). **Control** ITN as above and areas that had not yet received spraying during the study period and those for which the last spray round began more than 12 months ago. **Cointerventions:** intermittent preventive therapy
Outcomes	**Primary outcome** • Diagnostic positivity for malaria infection, expressed as the proportion of RDT-tested people who were found to be positive **Secondary outcome** • Indoor-outdoor distribution of human exposure to *An funestus* bites measured as bites per person per hour
Location profile	**Study location:** Luangwa located in Lusaka and Nyimba located in Eastern provinces, of the Republic of Zambia. Predominantly rural **Malaria endemicity:** perennial **EIR:** 70 (for non-users of LLINs) **Population proximity/density:** not reported ***Plasmodium* spp:***P falciparum*
Vector profile	**Primary (and secondary) vector species:***An funestus* **Vector behaviour (nature, stability, adult habitat, peak biting times, exophilic/endophilic, exophagic/endophagic, anthropophilic/zoophilic):** not reported **Phenotypic resistance profile:** F1 generation from wild-caught mosquitoes were exposed to standard WHO susceptibility tests using insecticide impregnated papers for the duration of the study (2010–2013). Throughout the study period, *An funestus* were consistently susceptible to both malathion and DDT (100% mortality) in both Luangwa and Nyimba. Moderate resistance to deltamethrin that increased to high resistance in both sites during the study period. Lambdacyhalothrin showed a similar pattern but was only measured in Luangwa. **Genotypic resistance profile:** not reported **Method of mosquito collection:** light traps and Ifakara tent traps. Each house was visited once per month for mosquito trapping. Light traps were placed at the foot end of an occupied sleeping space covered with an LLIN, hanging approximately 1.5 m above the floor. A tent trap was placed immediately outside, approximately 5 m away from the house. Traps were set up in the evenings and collection of the captured mosquitoes was done in the early morning by aspiration. Additionally, human landing catches were conducted both indoors and outdoors from 18.00 to 06.00 hours.
Notes	Note: due to the stepped wedge design and the way the results were reported in the paper, with data from different comparisons at different times conflated, we were unable to establish contemporaneous intervention and control groups between which we could compare malaria outcomes. We contacted the authors to request disaggregated data in order to make this comparison.

Omondi 2019

Methods	Observation of impact of implementation of IRS in 1 country compared to a second county in which no IRS was implemented.
Participants	Random samples of residents aged ≥ 6 months.
Interventions	Historically malaria control depended on LLINs. IRS with Actellic was conducted in intervention areas.
Outcomes	Malaria prevalence, anaemia prevalence, and parasite density
Location profile	2 counties with the highest malaria prevalence in Western Kenya
Vector profile	Not described
Notes	This information was taken from a conference abstract. We contacted the authors for further details regarding study design and period of observation to determine whether the trial meets the review's inclusion criteria. No response to date.

Soma 2021

Methods	Article reports a small entomological cross-sectional substudy, but references a larger RCT that may measure epidemiological outcomes in humans.
Participants	*An gambiae* mosquitoes (both wild and laboratory strains)
Interventions	IRS with microencapsulated formulation of pirimiphos-methyl and LLINs
Outcomes	Vector susceptibility and residual activity of the insecticide. It is stated in the article that the overall RCT aims to investigate whether the use of complementary strategies such as IRS together with LLINs affords additional reduction in malaria transmission and cases.
Location profile	Diébougou, southwest Burkina Faso
Vector profile	*An gambiae* (*s.l.*)
Notes	We contacted the authors for further details regarding the status of the RCT, methods used, and outcomes measured to determine whether the trial meets the review's inclusion criteria. No response to date.

Turnbull 2018

Methods	None described
Participants	No details
Interventions	IRS campaigns described in abstract but no details provided
Outcomes	Incidence of clinical malaria
Location profile	Kenyan highland areas of Kipsamoite and Kapsisiywa, areas of unstable transmission

Turnbull 2018 *(Continued)*

Vector profile	No details
Notes	This information was taken from a conference abstract. We contacted the authors for further details regarding study design and period of observation to determine whether the trial meets the review's inclusion criteria. No response to date.

Zogo 2019

Methods	4-armed RCT. LLIN + larviciding (8 villages) vs LLIN + IRS (6) vs LLIN + human behavioural change campaign (6) vs LLIN only (6)
Participants	Not described
Interventions	Larviciding with *Bacillus thuringiensis israeliensis* IRS with pyrimiphos-methyl Intensive communication for human behavioural changes LLINs distributed before the implementation of complementary strategies
Outcomes	Malaria incidence, malaria prevalence, and entomological outcomes
Location profile	28 villages in Korhogo area, Northern Cote d'Ivoire
Vector profile	Not described
Notes	This information was taken from a conference abstract. We contacted the authors for further details regarding study design and period of observation to determine whether the trial meets the review's inclusion criteria. No response to date.

An: *Anopheles*; CDC: Centers for Disease Control and Prevention; cRCT: cluster randomized controlled trial; DDT: dichloro-diphenyl-trichlorethane; EIR: entomological inoculation rate; ICT: immunochromatographic diagnostic test; IRS: indoor residual spraying; ITN: insecticide-treated net; ITT: intention to treat; LLIN: long-lasting insecticidal net; RCT: randomized controlled trial; RDT: rapid diagnostic test; WHO: World Health Organization.

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

Zhou 2020

Study name	Adaptive interventions for optimizing malaria control: an implementation study protocol for a block-cluster randomized, sequential multiple assignment trial
Methods	Longitudinal block-cluster sequential multiple assignment randomized trial (SMART) design with longitudinal outcome measures for 3 years. 2-stage trial, with 36 clusters in the initial stage. At the beginning of stage 1, all clusters will be randomized with equal probability to either LLIN, piperonyl butoxide-treated LLIN (PBO nets), or LLIN + IRS by block randomization based on their respective malaria risks. Intervention effectiveness will be evaluated with 12 months of follow-up. Clinical malaria will be monitored through active case surveillance. At end of 12-month follow-up, clusters will be assessed for "response" vs "non-response" to PBO nets or LLIN + IRS based on the change in clinical malaria incidence rate and a predefined threshold value of cost-effectiveness set by the Ministry of Health. At beginning of stage 2, if an intervention was effective in stage 1, then the intervention will be continued. Non-responders to stage 1 PBO net treatment will be randomized equally to either PBO nets + LSM (lar-

Zhou 2020 *(Continued)*	val source management) or an intervention determined by an enhanced reinforcement learning method. Similarly, non-responders to stage 1 LLIN + IRS treatment will be randomized equally to either LLIN + IRS + LSM or PBO nets + IRS. There will be an 18-month evaluation follow-up for stage 2 interventions.
Participants	Not described
Interventions	LLIN: Olyset and PermaNet 2.0 PBO nets: Olyset Plus LLIN IRS: Actellic LSM: the physical filling or removal of temporary larval habitats and the larviciding of semi-permanent and permanent habitats, per Kenya's National Malaria Strategic Plan. For the larviciding, the long-lasting microbial larvicide manufactured by Central Life Sciences with active ingredients *Bacillus thuringiensis israelensis* (Bti) (6% by weight) and *Bacillus sphaerius* (Bs) (1% by weight) will be used.
Outcomes	**Primary outcome** • Clinical malaria incidence rate **Secondary endpoints** • Malaria vector abundance and transmission intensity. Indoor and outdoor vector abundance will be measured using light traps • Cost-effectiveness of the interventions will be assessed using *Q*-learning
Starting date	
Contact information	
Notes	This is a protocol published in 2020 for a study that is scheduled to take > 3 years to complete.

DATA AND ANALYSES

Comparison 1. Non-pyrethroid-like indoor residual spraying (IRS) plus insecticide-treated nets (ITNs) versus ITNs alone

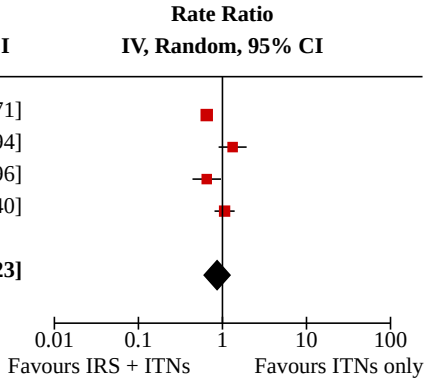
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Malaria incidence	4		Rate Ratio (IV, Random, 95% CI)	0.86 [0.61, 1.23]
1.2 Malaria incidence (net usage subgroup analysis)	3		Rate Ratio (IV, Random, 95% CI)	0.80 [0.53, 1.22]
1.2.1 High (≥ 80%)	2		Rate Ratio (IV, Random, 95% CI)	0.65 [0.60, 0.71]
1.2.2 Moderate (50–79%)	0		Rate Ratio (IV, Random, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2.3 Low (< 50%)	1		Rate Ratio (IV, Random, 95% CI)	1.32 [0.90, 1.94]
1.3 Malaria incidence (sensitivity analysis: exclusion of studies with high risk of bias)	3		Rate Ratio (IV, Random, 95% CI)	0.76 [0.55, 1.06]
1.4 Malaria parasite prevalence	5		Risk Ratio (IV, Random, 95% CI)	0.72 [0.47, 1.11]
1.5 Malaria parasite prevalence (sensitivity analysis: exclusion of studies with high risk of bias)	4		Risk Ratio (IV, Random, 95% CI)	0.61 [0.42, 0.88]
1.6 Anaemia prevalence	3		Risk Ratio (IV, Random, 95% CI)	0.71 [0.38, 1.31]
1.7 Anaemia prevalence (net usage subgroup analysis)	2		Risk Ratio (IV, Random, 95% CI)	0.50 [0.16, 1.60]
1.7.1 High (≥ 80%)	0		Risk Ratio (IV, Random, 95% CI)	Not estimable
1.7.2 Moderate (50–79%)	1		Risk Ratio (IV, Random, 95% CI)	0.33 [0.05, 1.99]
1.7.3 Low (< 50%)	1		Risk Ratio (IV, Random, 95% CI)	0.81 [0.37, 1.77]

Analysis 1.1. Comparison 1: Non-pyrethroid-like indoor residual spraying (IRS) plus insecticide-treated nets (ITNs) versus ITNs alone, Outcome 1: Malaria incidence

Study or Subgroup	log[Rate Ratio]	SE	Weight	Rate Ratio IV, Random, 95% CI
Chaccour 2021 (1)	-0.430783	0.042943	29.9%	0.65 [0.60 , 0.71]
Corbel 2012 (2)	0.2787	0.1959	22.3%	1.32 [0.90 , 1.94]
Kafy 2017 (3)	-0.4308	0.1991	22.1%	0.65 [0.44 , 0.96]
Loha 2019 (4)	0.0586	0.1406	25.6%	1.06 [0.80 , 1.40]
Total (95% CI)			**100.0%**	**0.86 [0.61 , 1.23]**

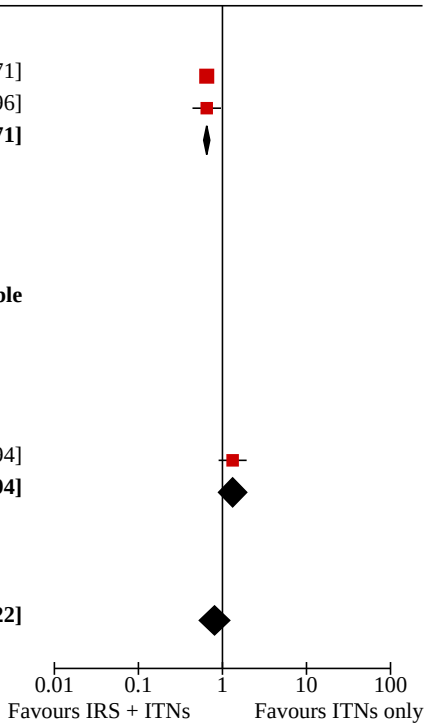
Heterogeneity: Tau² = 0.11; Chi² = 22.33, df = 3 (P < 0.0001); I² = 87%
Test for overall effect: Z = 0.82 (P = 0.41)
Test for subgroup differences: Not applicable



Footnotes
(1) IRS with pirimiphos-methyl
(2) IRS with bendiocarb
(3) IRS with bendiocarb (years 2 and 3)
(4) IRS with propoxur

Analysis 1.2. Comparison 1: Non-pyrethroid-like indoor residual spraying (IRS) plus insecticide-treated nets (ITNs) versus ITNs alone, Outcome 2: Malaria incidence (net usage subgroup analysis)

Study or Subgroup	log[Rate Ratio]	SE	Weight	Rate Ratio IV, Random, 95% CI
1.2.1 High (≥ 80%)				
Chaccour 2021 (1)	-0.430783	0.042943	40.0%	0.65 [0.60 , 0.71]
Kafy 2017 (2)	-0.4308	0.1991	29.9%	0.65 [0.44 , 0.96]
Subtotal (95% CI)			**69.9%**	**0.65 [0.60 , 0.71]**
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%				
Test for overall effect: Z = 10.26 (P < 0.00001)				
1.2.2 Moderate (50–79%)				
Subtotal (95% CI)				**Not estimable**
Heterogeneity: Not applicable				
Test for overall effect: Not applicable				
1.2.3 Low (< 50%)				
Corbel 2012 (3)	0.2787	0.1959	30.1%	1.32 [0.90 , 1.94]
Subtotal (95% CI)			**30.1%**	**1.32 [0.90 , 1.94]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.42 (P = 0.15)				
Total (95% CI)			**100.0%**	**0.80 [0.53 , 1.22]**
Heterogeneity: Tau² = 0.11; Chi² = 12.54, df = 2 (P = 0.002); I² = 84%				
Test for overall effect: Z = 1.03 (P = 0.30)				
Test for subgroup differences: Chi² = 12.54, df = 1 (P = 0.0004), I² = 92.0%				



Footnotes

(1) IRS with pirimiphos-methyl

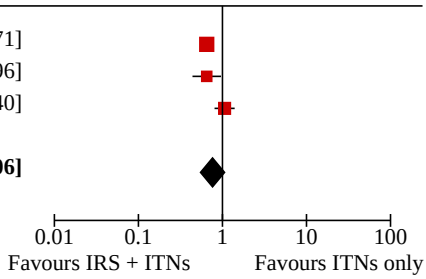
(2) IRS with bendiocarb (years 2 and 3)

(3) IRS with bendiocarb

Analysis 1.3. Comparison 1: Non-pyrethroid-like indoor residual spraying (IRS) plus insecticide-treated nets (ITNs) versus ITNs alone, Outcome 3: Malaria incidence (sensitivity analysis: exclusion of studies with high risk of bias)

Study or Subgroup	log[Rate Ratio]	SE	Weight	Rate Ratio IV, Random, 95% CI
Chaccour 2021 (1)	-0.430783	0.042943	41.0%	0.65 [0.60 , 0.71]
Kafy 2017 (2)	-0.4308	0.1991	26.4%	0.65 [0.44 , 0.96]
Loha 2019 (3)	0.0586	0.1406	32.5%	1.06 [0.80 , 1.40]
Total (95% CI)			**100.0%**	**0.76 [0.55 , 1.06]**

Heterogeneity: Tau² = 0.07; Chi² = 11.12, df = 2 (P = 0.004); I² = 82%
Test for overall effect: Z = 1.62 (P = 0.10)
Test for subgroup differences: Not applicable

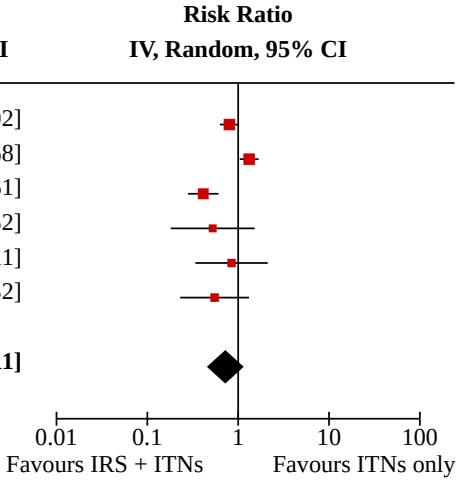


Footnotes
(1) IRS with pirimiphos-methyl
(2) IRS with bendiocarb (years 2 and 3)
(3) IRS with propoxur

Analysis 1.4. Comparison 1: Non-pyrethroid-like indoor residual spraying (IRS) plus insecticide-treated nets (ITNs) versus ITNs alone, Outcome 4: Malaria parasite prevalence

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Random, 95% CI
Chaccour 2021 (1)	-0.2231	0.1219	22.8%	0.80 [0.63 , 1.02]
Corbel 2012 (2)	0.2776	0.1216	22.8%	1.32 [1.04 , 1.68]
Kafy 2017 (3)	-0.8858	0.1971	20.5%	0.41 [0.28 , 0.61]
Protopopoff 2018 (4)	-0.6463	0.5423	9.9%	0.52 [0.18 , 1.52]
Protopopoff 2018 (5)	-0.1681	0.4679	11.7%	0.85 [0.34 , 2.11]
West 2014 (2)	-0.5978	0.4448	12.3%	0.55 [0.23 , 1.32]
Total (95% CI)			**100.0%**	**0.72 [0.47 , 1.11]**

Heterogeneity: Tau² = 0.20; Chi² = 28.51, df = 5 (P < 0.0001); I² = 82%
Test for overall effect: Z = 1.47 (P = 0.14)
Test for subgroup differences: Not applicable

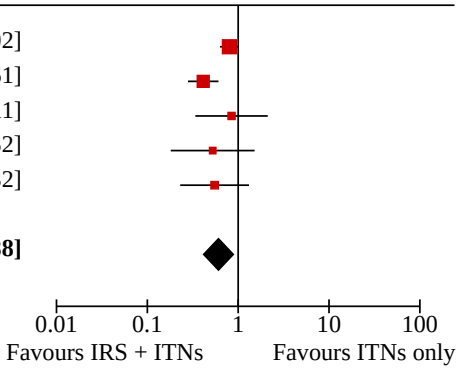


Footnotes
(1) IRS with pirimiphos-methyl
(2) IRS with bendiocarb
(3) IRS with bendiocarb (years 2 and 3)
(4) [Comparator: pyrethroid ITNs] IRS with pirimiphos-methyl
(5) [Comparator: pyrethroid-PBO net] IRS with pirimiphos-methyl

Analysis 1.5. Comparison 1: Non-pyrethroid-like indoor residual spraying (IRS) plus insecticide-treated nets (ITNs) versus ITNs alone, Outcome 5: Malaria parasite prevalence (sensitivity analysis: exclusion of studies with high risk of bias)

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Random, 95% CI
Chaccour 2021 (1)	-0.2231	0.1219	36.3%	0.80 [0.63 , 1.02]
Kafy 2017 (2)	-0.8858	0.1971	29.3%	0.41 [0.28 , 0.61]
Protopopoff 2018 (3)	-0.1681	0.4679	11.9%	0.85 [0.34 , 2.11]
Protopopoff 2018 (4)	-0.6463	0.5423	9.6%	0.52 [0.18 , 1.52]
West 2014 (5)	-0.5978	0.4448	12.8%	0.55 [0.23 , 1.32]
Total (95% CI)			**100.0%**	**0.61 [0.42 , 0.88]**

Heterogeneity: Tau² = 0.09; Chi² = 8.81, df = 4 (P = 0.07); I² = 55%
Test for overall effect: Z = 2.62 (P = 0.009)
Test for subgroup differences: Not applicable



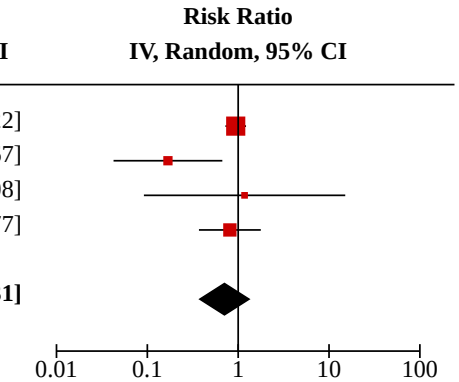
Footnotes

(1) IRS with pirimiphos-methyl
(2) IRS with bendiocarb (years 2 and 3)
(3) [Comparator: pyrethroid-piperonyl butoxide net] IRS with pirimiphos-methyl
(4) [Comparator: pyrethroid ITNs] IRS with pirimiphos-methyl
(5) IRS with bendiocarb

Analysis 1.6. Comparison 1: Non-pyrethroid-like indoor residual spraying (IRS) plus insecticide-treated nets (ITNs) versus ITNs alone, Outcome 6: Anaemia prevalence

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Random, 95% CI
Loha 2019 (1)	-0.0622	0.1332	50.5%	0.94 [0.72 , 1.22]
Protopopoff 2018 (2)	-1.7804	0.7034	14.8%	0.17 [0.04 , 0.67]
Protopopoff 2018 (3)	0.162	1.3019	5.3%	1.18 [0.09 , 15.08]
West 2014 (4)	-0.2107	0.3998	29.4%	0.81 [0.37 , 1.77]
Total (95% CI)			**100.0%**	**0.71 [0.38 , 1.31]**

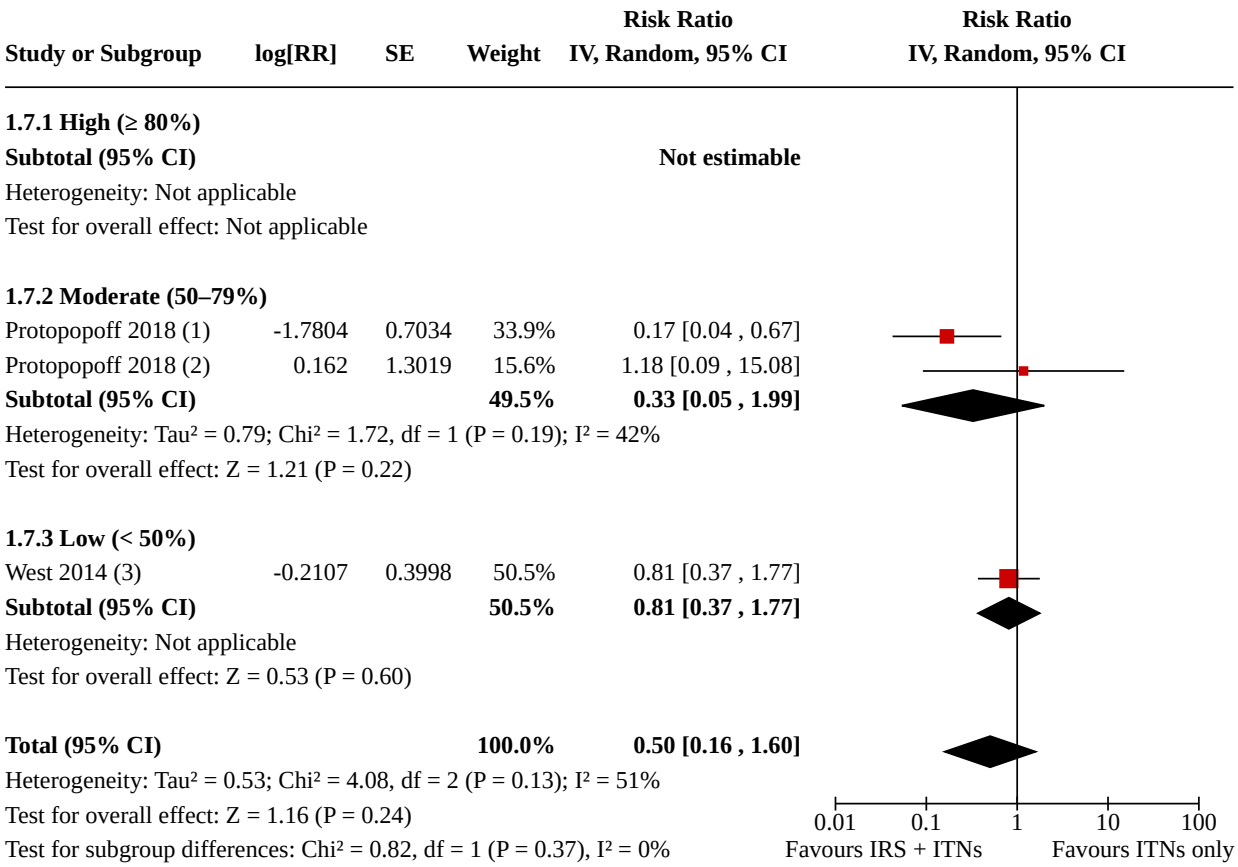
Heterogeneity: Tau² = 0.18; Chi² = 5.85, df = 3 (P = 0.12); I² = 49%
Test for overall effect: Z = 1.10 (P = 0.27)
Test for subgroup differences: Not applicable



Footnotes

(1) [Haemoglobin < 11 g/dL] IRS with propoxur
(2) [Haemoglobin < 8 g/dL; comparator: pyrethroid net] IRS with pirimiphos-methyl
(3) [Haemoglobin < 8 g/dL; comparator: pyrethroid-piperonyl butoxide net] IRS with pirimiphos-methyl
(4) [Haemoglobin < 8 g/dL] IRS with bendiocarb

Analysis 1.7. Comparison 1: Non-pyrethroid-like indoor residual spraying (IRS) plus insecticide-treated nets (ITNs) versus ITNs alone, Outcome 7: Anaemia prevalence (net usage subgroup analysis)



Footnotes

(1) [Haemoglobin < 8 g/dL; comparator: Pyrethroid net] IRS with Pirimiphos-methyl

(2) [Haemoglobin < 8 g/dL; comparator: pyrethroid-piperonyl butoxide net] IRS with pirimiphos-methyl

(3) [Haemoglobin < 8 g/dL] IRS with bendiocarb

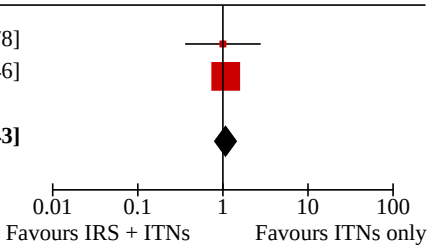
Comparison 2. Pyrethroid-like indoor residual spraying (IRS) plus insecticide-treated nets (ITNs) versus ITNs alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Malaria incidence	2		Rate Ratio (IV, Random, 95% CI)	1.07 [0.80, 1.43]
2.2 Malaria parasite prevalence	3		Risk Ratio (IV, Random, 95% CI)	1.11 [0.86, 1.44]
2.3 Anaemia prevalence	1		Risk Ratio (IV, Random, 95% CI)	1.12 [0.89, 1.40]

Analysis 2.1. Comparison 2: Pyrethroid-like indoor residual spraying (IRS) plus insecticide-treated nets (ITNs) versus ITNs alone, Outcome 1: Malaria incidence

Study or Subgroup	log[Rate Ratio]	SE	Weight	Rate Ratio IV, Random, 95% CI
Kafy 2017 (1)	0	0.5213	7.9%	1.00 [0.36 , 2.78]
Pinder 2015 (2)	0.077	0.1531	92.1%	1.08 [0.80 , 1.46]
Total (95% CI)			**100.0%**	**1.07 [0.80 , 1.43]**

Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.89); I² = 0%
Test for overall effect: Z = 0.48 (P = 0.63)
Test for subgroup differences: Not applicable

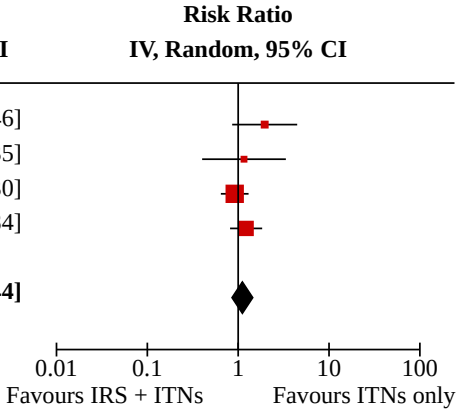


Footnotes
(1) IRS with deltamethrin (year 1)
(2) IRS with diphenyl-trichlorethane

Analysis 2.2. Comparison 2: Pyrethroid-like indoor residual spraying (IRS) plus insecticide-treated nets (ITNs) versus ITNs alone, Outcome 2: Malaria parasite prevalence

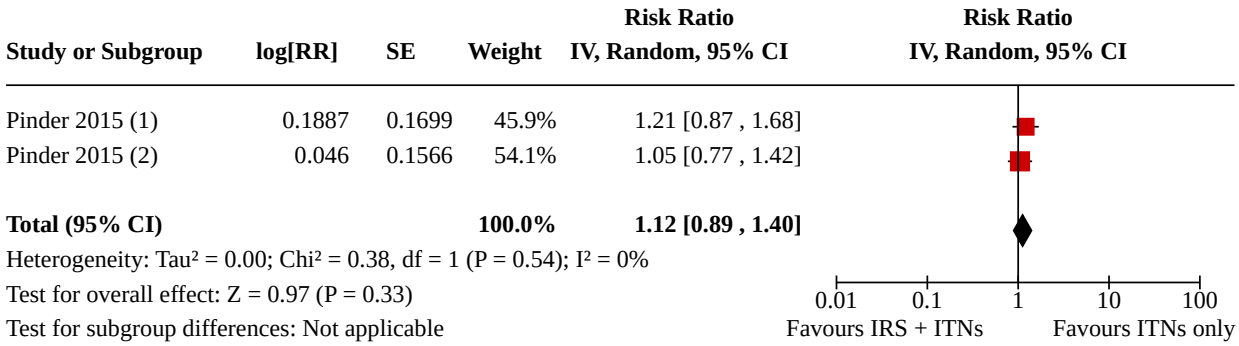
Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Random, 95% CI
Kafy 2017 (1)	0.6719	0.4203	9.7%	1.96 [0.86 , 4.46]
Keating 2011 (2)	0.1476	0.5413	5.9%	1.16 [0.40 , 3.35]
Pinder 2015 (3)	-0.0879	0.1792	47.6%	0.92 [0.64 , 1.30]
Pinder 2015 (4)	0.2013	0.2075	36.8%	1.22 [0.81 , 1.84]
Total (95% CI)			**100.0%**	**1.11 [0.86 , 1.44]**

Heterogeneity: Tau² = 0.01; Chi² = 3.20, df = 3 (P = 0.36); I² = 6%
Test for overall effect: Z = 0.80 (P = 0.42)
Test for subgroup differences: Not applicable



Footnotes
(1) IRS with deltamethrin (year 1)
(2) IRS with diphenyl-trichlorethane
(3) [2011] IRS with diphenyl-trichlorethane
(4) [2010] IRS with diphenyl-trichlorethane

Analysis 2.3. Comparison 2: Pyrethroid-like indoor residual spraying (IRS) plus insecticide-treated nets (ITNs) versus ITNs alone, Outcome 3: Anaemia prevalence



Footnotes

(1) [2011] IRS with diphenyl-trichlorethane

(2) [2010] IRS with diphenyl-trichlorethane

ADDITIONAL TABLES

Table 1. World Health Organization – recommended insecticides for indoor residual spraying against malaria vectors

Insecticides and formulations	Dosage (g AI/m²)
DDT WP	1–2
Malathion WP	2
Fenitrothion WP	2
Pirimiphos-methyl WP, EC	1–2
Pirimiphos-methyl CS	1
Bendiocarb WP, WP-SB	0.1–0.4
Propoxur WP	1–2
Alpha-cypermethrin WP, SC, WG-SB	0.02–0.03
Bifenthrin WP	0.025–0.05
Cyfluthrin WP	0.02–0.05
Deltamethrin WP, WG, WG-SB, SC-PE	0.02–0.025
Etofenprox WP	0.1–0.3
Lambda-cyhalothrin WP, CS	0.02–0.03

AI: active ingredient; CS: capsule suspension; DDT: dichloro-diphenyl-trichlorethane; EC: emulsifiable concentrate; SC: suspension concentrate; SC-PE: polymer-enhanced suspension concentrate; WG: water-dispersible granule; WG-SB: water-dispersible granules packaged in water-soluble bags; WP: wettable powder; WP-SB: wettable powder in sealed water-soluble bags.

Table 2. World Health Organization – recommended long-lasting insecticidal nets

Product name	Product type	Status of WHO recommendation
DawaPlus 2.0	Deltamethrin coated on polyester	Interim
Duranet	Alpha-cypermethrin incorporated into polyethylene	Full
Interceptor	Alpha-cypermethrin coated on polyester	Full
LifeNet	Deltamethrin incorporated into polypropylene	Interim
MAGNet	Alpha-cypermethrin incorporated into polyethylene	Full
MiraNet	Alpha-cypermethrin incorporated into polyethylene	Interim
Olyset Net	Permethrin incorporated into polyethylene	Full
Olyset Plus	Permethrin and PBO incorporated into polyethylene	Interim
Panda Net 2.0	Deltamethrin incorporated into polyethylene	Interim
PermaNet 2.0	Deltamethrin coated on polyester	Full
PermaNet 3.0	Combination of deltamethrin coated on polyester with strengthened border (side panels), and deltamethrin and PBO incorporated into polyethylene (roof)	Interim
Royal Sentry	Alpha-cypermethrin incorporated into polyethylene	Full
SafeNet	Alpha-cypermethrin coated on polyester	Full
Veeralin	Alpha-cypermethrin and PBO incorporated into polyethylene	Interim
Yahe	Deltamethrin coated on polyester	Interim
Yorkool	Deltamethrin coated on polyester	Full

LLIN: long-lasting insecticidal nets; PBO: piperonyl butoxide.
Adapted from WHO 2014b.

Table 3. World Health Organization – recommended insecticide products for treatment of mosquito nets for malaria vector control

Insecticide	Formulation	Dosage (mg AI/m^2 of netting)
Alpha-cypermethrin	SC 10%	20–40
Cyfluthrin	EW 5%	50
Deltamethrin	SC 1%; WT 25%; and WT 25% + binder	15–25

Table 3. World Health Organization – recommended insecticide products for treatment of mosquito nets for malaria vector control *(Continued)*

Etofenprox	EW 10%	200
Lambda-cyhalothrin	CS 2.5%	10–15
Permethrin	EC 10%	200–500
ICON MAXX (long-lasting lambda-cyhalothrin formulation)	CS 10% + binder	50–83

AI: active ingredient; EC: emulsifiable concentrate; EW: emulsion, oil in water; CS: capsule suspension; SC: suspension concentrate; WT: water dispersible tablet.
Adapted from WHO 2014c.

Table 4. Characteristics of indoor residual spraying

Study	AI, formulation, and dose	Frequency of application	Coverage	Who carried out the spraying	Vector species
Comparison 1: IRS using non-pyrethroid-like insecticides plus ITNs vs ITNs alone					
Chaccour 2021	Pirimiphos-methyl (Actellic 300 CS) 1 g AI/m^2	Annually, October–November 2016 and 2017	2016: 83% 2017: 85%	President's Malaria Initiative Africa Indoor Residual Spraying (PMI AIRS)	*An gambiae s.l.* and *An funestus s.l.*
Corbel 2012	Bendiocarb 80% wettable powder (FICAM 80, Bayer) 400 mg/mU	Every 8 months, June 2008 to December 2009	Aimed for 80%; actual coverage was 92%	Unreported	*An gambiae s.l.* and *An funestus s.l.*
Gogue 2020	Pirimiphos-methyl (Actellic 300 CS) 1 g AI/m^2	Once, August–September 2017	95.6–96.9%	AngloGold Ashanti Malaria Control Programme (AGAMal)	*An gambiae s.l.* and *An funestus*
Kafy 2017 (Years 2 and 3)	Bendiocarb 80% wettable powder (FICAM 80, Bayer) 200 mg/m^2	Twice a year, August and late December, 2013 and 2014	2013: 82% 2014: 83%	Unreported	*An arabiensis* and *An funestus s.l.*
Namuganga 2021 (Years 1, 2, and 3)	Bendiocarb	Twice a year, December 2014 to February 2015; June–July 2015; November–December 2015	96.9% (Nagongera district)	Unreported	*An gambiae* and *An arabiensis*
Namuganga 2021 (Years 4 and 5)	Pirimiphos-methyl (Actellic 300 CS)	Annually	Unreported	Unreported	*An gambiae* and *An arabiensis*

Table 4. Characteristics of indoor residual spraying *(Continued)*

Loha 2019	Propoxur	Annually, prior to transmission season (September 2014, July 2015, July 2016)	95–96%	Locally recruited spray personnel and supervisors	*An arabiensis* and *An pharoensis*
Protopopoff 2018	Pirimiphos-methyl 30% capsule suspension (Actellic 300CS) 1 g AI/m^2	Once, February 2015	Standard ITN arm: 0.5% (95% CI 0.1 to 2.0) Standard ITN + IRS arm: 94% (95% CI 92 to 96) Pyrethroid-PBO net arm: 4% (95% CI 0.5 to 29) Pyrethroid-PBO net + IRS arm: 94% (95% CI 87 to 97) Buffer size between clusters: minimum outer buffer zone of 300 m. Only the inner core area was used for the measurement of study outcomes	Unreported	*An gambiae s.s.*, *An arabiensis* and *An funestus*
West 2014	Bendiocarb 80% wettable powder (FICAM 80, Bayer) 400 mg/m^2	Twice, December 2011 to January 2012 and April 2012 to May 2012	Aimed for 80% (actual coverage was 89.3–92.1%)	RTI International on behalf of PMI	*An gambiae s.s.* and *An arabiensis*
Comparison 2: IRS using pyrethroid-like insecticides plus ITNs vs ITNs alone					
Kafy 2017 (Year 1)	Deltamethrin (25 mg/m^2, formulation not reported, Chema Industries)	Twice, in August and late December 2012	99%	Unreported	*An gambiae s.l.* and *An funestus s.l.*
Keating 2011	DDT wettable powder 1–2 g AI/m^2	Once, June–July 2009	Aimed for 80% (84.8% of households sampled sprayed within 12 months)	Unreported	*An arabiensis* and *An gambiae s.s.*
Pinder 2015	DDT 75% wettable powder (Hindustan Insecticides) 2 g AI/m^2	Once per year, July 2010 and July–August 2011	Aimed for 80% (actual coverage was 83–86%)	Operators from the Gambian National Malaria Control Programme and team leaders from the regional health team	*An gambiae s.l.*

AI: active ingredient; *An arabiensis*: *Anopheles arabiensis; An funestus*: *Anopheles funestus*; *Angambiae*: *Anopheles gambiae*; *An pharoensis*: *Anopheles pharoensis*; CI: confidence interval; DDT: dichloro-diphenyl-trichlorethane; IRS: indoor residual spraying; ITN: insecticide-treated net; PBO: piperonyl butoxide.

Table 5. Insecticide-treated net coverage and compliance

Study	**Arm**	ITN ownership:	**ITN use:**

Table 5. Insecticide-treated net coverage and compliance *(Continued)*

		% of households with **≥ 1** ITN (unless otherwise stated)[a]	**% individuals using an ITN the previous night (unless otherwise stated)[a]**
Comparison 1: IRS using non-pyrethroid-like insecticides plus ITNs vs ITNs alone			
Chaccour 2021	Control	**High**	**High**
	Intervention	2017: 54% 2018: 95%	92 to 94%
Corbel 2012	Control	**Not rated** Not reported. Proportion of sleeping spaces protected by ITN: 38% (95% CI 36 to 41)	**Low** 43% (40 to 45)
	Intervention	**Not rated** Not reported. Proportion of sleeping spaces protected by ITN: 45% (95% CI 43 to 48)	**Low** 43% (40 to 46)
Gogue 2020	Both arms	**High** 2016: 93.9%	**Moderate** 2016: 63.2% (all ages); 75.5% (children aged < 5 years)
Kafy 2017	Control	**High** 2013: 82.1% 2014: 98.6%	**High** 2013: 74% 2014: 82%
	Intervention		**High** 2013: 75% 2014: 82%
Namuganga 2021	N/A. Measurements reported are for Nagongera study site. ITN ownership and use in the remaining 4 sites was not reported	**High** 2013: 71.0% 2015: 95.5%	**High** 99%
Loha 2019	Control	**High** At baseline: 100%	**Not rated** Not reported. Proportion of households where ≥ 1 member used an ITN the previous night: weeks 1–26: 49%; weeks 26–53: 27%; weeks 53–79: 6%;

Table 5. Insecticide-treated net coverage and compliance *(Continued)*

			weeks 79–121: 1%
	Intervention		**Not rated** Not reported. Proportion of households where ≥ 1 member used an ITN the previous night: weeks 1–26: 47%; weeks 26–53: 26%; weeks 53–79: 8%; weeks 79–121: 1%
Protopopoff 2018	Standard ITNs	**High** At 9 months' postintervention: 97% (95% CI 93 to 99)	**High** At 9 months' postintervention: 80% (95% CI 75 to 85)
	Standard ITNs + IRS	**Moderate** At 9 months' postintervention: 76% (95% CI 70 to 80)	**Moderate** At 9 months' postintervention: 76% (95% CI 70 to 80)
	Pyrethroid-PBO net	**High** At 9 months' postintervention: 98% (95% CI 97 to 99)	**Moderate** At 9 months' postintervention: 78% (95% CI 73 to 82)
	Pyrethroid-PBO net + IRS	**High** At 9 months' postintervention: 98% (95% CI 95 to 99)	**Moderate** At 9 months' postintervention: 77% (95% CI 70 to 83)
West 2014	Control	**Not rated** Not reported. Proportion of households with 1 ITN per sleeping space: February–March: 52.2 (95% CI 47.8 to 56.5); June–July: 51.6 (95% CI 47 to 56); October–December: 52.8 (95% CI 47.6 to 58)	**Low** February–March: 46.6 (95% CI 41.7 to 51.6); June–July: 40.7 (95% CI 34.7 to 47); October–December: 36 (95% CI 29.8 to 42.6)
	Intervention	**Not rated** Not reported. Proportion of households with 1 ITN per sleeping space: February–March: 57.2 (95% CI 53.6 to 60.7) June–July: 57.4 (95% CI 54 to 60.9) October–December: 56.8 (95% CI 51.7 to 61.8)	**Low** February–March: 53 (95% CI 47.5 to 58.3) June–July: 44.1 (95% CI 39.2 to 49.2) October–December: 36.1 (95% CI 31 to 41.5)
Comparison 2: IRS using pyrethroid-like insecticides plus ITNs vs ITNs alone			

Table 5. Insecticide-treated net coverage and compliance *(Continued)*

Kafy 2017	Control	**High** 99.6%	**High** 79%
	Intervention		**High** 79%
Keating 2011	Control	**Not rated** Not reported. Proportion of people living in household with ≥ 1 ITN: 72% (95% CI 70.2 to 73.7)	**Low** Mean: 46.2 (95% CI 43.9 to 48.6)
	Intervention	**Not rated** Not reported. Proportion of people living in household with ≥ 1 ITN: 75.8% (95% CI 74.2 to 77.4)	**Moderate** Mean: 50.7% (95% CI 48.6 to 52.8)
Pinder 2015	Control	**Not rated** Not reported	**High** Mean average across all clusters: 2011: 92% 2012: 96%
	Intervention		**High** Mean average across all clusters: 2011: 89% 2012: 93%

CI: confidence interval; IRS: indoor residual spraying; ITN: insecticide-treated net; LLIN: long-lasting insecticidal net.
[a]ITN ownership and use rating cut-offs prespecified in protocol (high: > 80%; moderate: 50–79%; low: < 50%).

Table 6. Malaria incidence data from quasi-experimental design studies

Study	Study design	Outcome	IRS + ITNs	ITNs alone	Measure of estimate of effect	Estimate of effect
Comparison 1: IRS using non-pyrethroid-like insecticides + ITNs vs ITNs alone						
Gogue 2020	Controlled before-after	Change in cumulative incidence from 6 months peak in 2016 (before intervention) to equivalent period in 2017 (after intervention)	−42% (95% CI 28% to 56%)	−5% (95% CI −6% to 15%)	Difference in differences	37% (95% CI 18 to 57%) greater reduction in incidence observed in intervention arm; favouring IRS
Namuganga 2021	Interrupted time series	Mean monthly confirmed cases of malaria (adjusted for testing rate)	894 (59 months post-IRS	2446 (12 months pre-IRS)	Rate ratio	0.15 (0.12 to 0.18); favouring IRS (fourth and fifth year post IRS)

IRS: indoor residual spraying.

Table 7. Entomological inoculation rate results

Trial	Methods of EIR measurement	Comparison	Mean EIR (95% CI)	
			IRS + ITNs	ITNs alone
Comparison 1: IRS using non-pyrethroid-like insecticides + ITNs vs ITNs alone				
Chaccour 2021	Mean number of infectious bites per household per month	IRS with standard ITN vs standard ITN alone	0.28 (0.08 to 0.60)	0.57 (0.28 to 1.00)
Corbel 2012	Mean number of infected bites per person per year (estimated from the number of anopheline vectors caught using human landing catches and the proportion of anopheline vectors infective)	IRS with standard ITN vs standard ITN alone	7.3 (3.8 to 14.2)	9.4 (5.1 to 17.1)
Protopopoff 2018	Mean number of infected bites per household per night (the number of infective anopheline vectors caught using light traps in 1 night per month was used as a proxy for this)	IRS with standard ITN vs standard ITN alone	0.05 (n = 413)	1.76 (n = 449)
		IRS with pyrethroid-PBO net vs pyrethroid-PBO net alone	0.00 (n = 459)	0.26 (n = 452)
West 2014	Mean number of infected bites per household per month (estimated from the number of infective anopheline vectors caught using light traps in 1 night)	IRS with standard ITN vs standard ITN alone	1.3 (0.4 to 4.4)	1.1 (0.4 to 2.8)
Comparison 2: IRS using pyrethroid-like insecticides + ITNs vs ITNs alone				
Pinder 2015	Mean number of infected bites per person per transmission season (estimated from the number of anopheline vectors caught using light traps and the proportion of anopheline vectors infective)	IRS with standard ITN vs standard ITN alone: 2010	1.08 (0.16 to 4.02)	2.44 (0.69 to 6.39)
		IRS with standard ITN vs standard ITN alone: 2011	0.29 (0.00 to 2.66)	1.45 (0.15 to 5.69)

CI: confidence interval; EIR: entomological inoculation rate; IRS: indoor residual spraying; ITN: insecticide-treated net; n: number of participants; PBO: piperonyl butoxide.

Table 8. Sporozoite rate results

Trial	Assessment method	Comparison	Reported results		Effect size (95% CIs)	
			IRS + ITNs	ITNs alone	IRS + ITNs	ITNs alone
Comparison 1: IRS using non-pyrethroid-like insecticides plus ITNs vs ITNs alone						
Corbel 2012	% of *An gambiae s.l.* caught from human landing catches with sporozoites (ELISA)	IRS with standard ITN vs standard ITN alone	3.22% (95% CI 1.76 to 4.68)	2.83% (95% CI 1.69 to 3.97)	Not reported	

Table 8. Sporozoite rate results *(Continued)*

Loha 2019	% of *An arabiensis* caught from light trap catches, pyrethrum spray catches, artificial outdoor pit shelters and human landing catches with sporozoites (ELISA)	IRS with standard ITN vs standard ITN alone	0% (0/238)	0% (0/78)	
Protopopoff 2018	% of *An gambiae s.l.* caught from light traps with sporozoites (ELISA)	IRS with standard ITN vs standard ITN alone	0.4% (1/269)	2.8% (19/683)	
		IRS with pyrethroid-PBO net vs pyrethroid-PBO net alone	0.0% (0/343)	0.7% (2/305)	
West 2014		IRS with standard ITN vs standard ITN alone	1.8% (95% CI 0.5 to 6.2; n = 717)	2.5% (95% CI 2.1 to 3.1; n = 3059)	OR 0.72 (0.21 to 2.53)
Comparison 2: IRS using pyrethroid-like insecticides plus ITNs vs ITNs alone					
Pinder 2015	% of *An gambiae s.l.* caught from light traps with sporozoites (ELISA)	IRS with standard ITN vs standard ITN alone: 2010	0.19% (4/2131)	0.32% (9/2829)	RR 0.59 (0.18 to 1.91)
		IRS with standard ITN vs standard ITN alone: 2011	0.65% (5/773)	0.09% (1/1131)	RR 7.32 (0.86 to 62.5)

An arabiensis: *Anopheles arabiensis; Angambiae*: *Anopheles gambiae*; CI: confidence interval; ELISA: enzyme-linked immunosorbent assay; IRS: indoor residual spraying; ITN: insecticide-treated net; MD: mean difference; OR: odds ratio; PBO: piperonyl butoxide; RR: risk ratio.
[a]Not adjusted for clustering.

Table 9. Adult mosquito density results

Trial	Methods of adult mosquito density measurement	Comparison	Reported results Mean (95% CIs)		Effect size (95% CIs)
			IRS + ITNs	ITNs alone	
Comparison 1: IRS using non-pyrethroid-like insecticides + ITNs vs ITNs alone					
Chaccour 2021	Average number of mosquitoes collected per trap night (CDC Light trap)	IRS with standard ITN vs standard ITN alone: *An funestus*	0.57 (0.52 to 0.62)	1.34 (1.22 to 2.46)	Rate ratio 0.52 (0.41 to 0.67)
		IRS with standard ITN vs standard ITN alone: *An gambiae s.l.*	0.08 (0.07 to 0.10)	0.15 (0.13 to 0.18)	Rate ratio 0.66 (0.47 to 0.93)
Corbel 2012	Mean number of bites per person per year from human landing catches	IRS with standard ITN vs standard ITN alone	228 (149 to 348; n = 896)	331 (218 to 504; n = 896)	Rate ratio 0.69 (0.38 to 1.25)

Table 9. Adult mosquito density results *(Continued)*

	(16 person-nights per village (total 28 villages divided evenly into 4 arms) per survey (total 8 surveys))				
Namuganga 2021	Human biting rate (number of female *Anopheles* mosquitoes captured per house-night of collection)	IRS with standard ITN vs standard ITN alone	3.23	18.71	Rate ratio 0.29 (0.17 to 0.50)
Loha 2019	Indoor host seeking density (mosquitoes per trap per night (592 person-nights per arm)	IRS with standard ITN vs standard ITN alone	0.09 (0.05 to 0.15)	0.03 (0.01 to 0.08)	Not reported
	Indoor resting density (mosquitoes per house per night) (560 person-nights per arm)		0.34 (0.24 to 0.47)	0.06 (0.03 to 0.12)	
	Outdoor resting density (mosquitoes per pit per day) (224 collection days per arm)		0.43 (0.27 to 1.69)	0.04 (0.01 to 0.15)	
	Indoor human biting rate (based on light trap catches)		0.26 (0.19 to 0.37)	0.10 (0.06 to 0.17)	
	Indoor human biting rate (based on human landing catches)		3.95 (2.39 to 6.53)	1.63 (0.92 to 2.89)	
	Outdoor human biting rate (based on artificial outdoor pit shelters)		4.16 (2.52 to 6.86)	1.68 (0.95 to 2.97)	
Protopopoff 2018	Mean number of vectors caught in light traps per night per household (7 randomly selected houses per cluster (total 48 clusters divided evenly into 4 arms) for 1 night per month (total 8 months))	IRS with standard ITN vs standard ITN alone	2.37 (n = 425)	2.83 (n = 471)	Not reported
		IRS with pyrethroid-PBO net vs pyrethroid-PBO net alone	1.85 (n = 493)	1.84 (n = 468)	
West 2014	Mean number of *An gambiae s.l.* per house per night (8 randomly selected houses per cluster (total 40 clusters divided evenly into 2 arms) for 1 night per month (total 21 months))	IRS with standard ITN vs standard ITN alone	0.4 (0.1 to 1.4; n = 1893)	1.7 (0.5 to 6.4; n = 1892)	Rate ratio 0.23 (0.04 to 1.44)
Comparison 2: IRS using pyrethroid-like insecticides + ITNs vs ITNs alone					
Pinder 2015	Mean number of *An gambiae s.l.* per trap per night (6 sentinel rooms in 32 clusters)	IRS with standard ITN vs standard ITN alone: 2010 light traps	3.70 (2.03 to 5.37)	4.92 (3.05 to 6.79)	MD −1.22 (−3.58 to 1.14)
		IRS with standard ITN vs standard ITN alone: 2010 exit traps	0.40 (−0.15 to 0.66)	0.54 (0.18 to 0.89)	MD −0.13 (−0.54 to 0.28)

Table 9. Adult mosquito density results *(Continued)*

IRS with standard ITN vs standard ITN alone: 2011 light traps	1.27 (0.39 to 2.15)	1.96 (0.69 to 3.24)	MD −0.69 (−2.15 to 0.77)
IRS with standard ITN vs standard ITN alone: 2011 exit traps	0.06 (0.01 to 0.10)	0.46 (−0.23 to 1.15)	MD −0.40 (−1.05 to 0.25)

An funestus: *Anopheles funestus*; *Angambiae*: *Anopheles gambiae*; CI: confidence interval; IRS: indoor residual spraying; ITNs: insecticide-treated nets; MD: mean difference; PBO: piperonyl butoxide.

Table 10. Prespecified changes to protocol for review update (received editorial approval: 4 December 2020)

Protocol section	Changes	Justification
Criteria for considering studies for this review: types of interventions	Only studies with ≥ 50% ITN coverage (defined as the proportion of households owning ≥ 1 ITN) in both study arms were considered suitable for inclusion.	The review aims to evaluate the impact of IRS when added to communities that are currently using ITNs. With unreported or low coverage rates, it would be unclear if we are examining the effect of IRS added to communities using nets or of IRS added to failing net programmes. This change is in line with the WHO Guidelines for Malaria Vector Control which state that IRS should not be used to compensate for poor implementation of a second intervention (WHO 2019).
Search methods for identification of studies: electronic searches	The previous search strategy was dependent on study titles or abstracts referring to both ITNs and IRS. We revised our search strategy so that studies that referred to IRS but did not mention ITNs in the title or abstract were also detected, so long as they were published after 2000, when ITN programmes began to be implemented as policy. The use of ITNs remained an inclusion criterion, and was confirmed during full text screening.	As ITNs are a core vector control strategy that is implemented as standard in many malaria transmission areas, the previous search strategy led to the potential dismissal of studies that evaluated the impact of IRS in areas where high ITN use was considered a given and was therefore not described in the title or abstract.

IRS: indoor residual spraying; ITN: insecticide-treated net; WHO: World Health Organization.

APPENDICES

Appendix 1. Search strategies

Cochrane Central Register of Controlled Trials

Issue 3 of 12, April 2019

ID Search Hits

#1 MeSH descriptor: [Malaria] explode all trees

#2 malaria:ti,ab,kw (Word variations have been searched)

#3 anopheles

#4 MeSH descriptor: [Anopheles] explode all trees

#5 mosquito*

#6 #1 or #2 or #3 or #4 or #5

#7 "indoor residual spray"

#8 "indoor residual spraying"

#9 "house spray*"

#10 IRS

#11 malathion or fenitrothion or pirimiphos-methyl or bendiocarb or propoxur or alpha-cypermethrin or bifenthrin or cyfluthrin or deltamethrin or etofenprox or lambda-cyhalothrin or DDT

#12 MeSH descriptor: [Insecticides] explode all trees and with qualifier(s): [Administration & dosage - AD, Supply & distribution - SD, Therapeutic use - TU]

#13 MeSH descriptor: [Pyrethrins] explode all trees and with qualifier(s): [Administration & dosage - AD, Supply & distribution - SD, Therapeutic use - TU]

#14 #7 or #8 or #9 or #10 or #11 or #12 or #13

#15 Net* or bednet* or ITN* or LLIN* or "Insecticide-Treated Bednet*" or "Insecticide-Treated net*"

#16 MeSH descriptor: [Insecticide-Treated Bednets] explode all trees

#17 #15 or #16

#18 #6 and #14 and #17

PubMed

PubMed search set	Search terms
1	Malaria [Mesh], Title/Abstract
2	Mosquito* Title/Abstract
3	"Anopheles"[Mesh]
4	1 or 2 or 3
5	“indoor residual spraying” or IRS* Title/Abstract
6	“house spray*” Title/Abstract
7	("Insecticides/administration and dosage"[Mesh] or "Insecticides/supply and distribution"[Mesh] or "Insecticides/therapeutic use"[Mesh]) or "Pyrethrins"[Mesh]
8	malathion or fenitrothion or pirimiphos-methyl or bendiocarb or propoxur or alpha-cypermethrin or bifenthrin or cyfluthrin or deltamethrin or etofenprox or lambda-cyhalothrin or DDT Title/Abstract
9	“insecticide-treated bednet*” or insecticide-treated net*” or “Long-lasting insecticidal net*” or LLIN* or ITN* or LN*or “bed net*”or “long-lasting net*” Title/Abstract
10	“Insecticide-Treated Bednets” [Mesh]

(Continued)

11	("Mosquito Control/instrumentation"[Mesh] OR "Mosquito Control/methods"[Mesh])
12	5 or 6 or 7 or 8
13	9 or 10 or 11
14	4 and 12 and 13
15	"Randomized Controlled Trial" [Publication Type] OR "Controlled Clinical Trial" [Publication Type]
16	single-blind* or double-blind* Title/Abstract
17	randomized or placebo or trial or groups or randomly Title/Abstract
18	"before and after " Title/Abstract
19	"Epidemiologic Studies"[Mesh]
20	"time series" Title/Abstract
21	20 OR 19 OR 18 OR 17 OR 16 OR 15
22	21 AND 14

Embase

1 malaria/ or malaria.mp.

2 Anopheles/ or anopheles.mp.

3 mosquito*.mp. or mosquito/

4 1 or 2 or 3

5 indoor residual spraying.mp. or indoor residual spraying/

6 indoor residual spray.mp.

7 house spray.mp.

8 house spraying.mp.

9 IRS.ab. or IRS.ti.

10 (malathion or fenitrothion or pirimiphos-methyl or bendiocarb or propoxur or alpha-cypermethrin or bifenthrin or cyfluthrin or deltamethrin or etofenprox or lambda-cyhalothrin or DDT).mp.

11 insecticide/ct, ad, cb, cm, dt [Clinical Trial, Drug Administration, Drug Combination, Drug Comparison, Drug Therapy]

12 pyrethroid/ct, ad, cb, cm, dt [Clinical Trial, Drug Administration, Drug Combination, Drug Comparison, Drug Therapy]

13 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12

14 4 and 13

15 (Net* or bednet* or ITN* or LLIN* or "Insecticide-Treated Bednet*" or "Insecticide-Treated net*").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]

16 bed net/

17 insecticide treated net/

18 15 or 16 or 17

19 14 and 18

20 randomized controlled trial/ or controlled clinical trial/

21 (randomized or randomised or placebo or double-blind* or single-blind*).mp.

22 epidemiology/

23 (before and after study).mp

24 time series.mp. or time series analysis/

25 field study.mp. or field study/

26 prospective study.mp. or prospective study/

29 20 or 21 or 22 or 23 or 24 or 27 or 28

30 19 and 29

LILACS

(tw:(indoor residual spraying OR irs OR house spraying)) AND (tw:(bednets OR nets OR itn)) AND (tw:(malaria OR mosquito OR anopheles)) AND (tw:(randomized OR controlled OR trial OR comparison OR compared))

WHAT'S NEW

Date	Event	Description
6 January 2022	New citation required and conclusions have changed	We updated the date of search to 8 November 2021.
6 January 2022	New search has been performed	Prespecified changes to the protocol for this review update received editorial approval on 4 December 2020. A summary of the changes made and justification for the changes are provided in Table 10.

HISTORY

Protocol first published: Issue 6, 2017
Review first published: Issue 5, 2019

Date	Event	Description
23 August 2019	Amended	Amended text in ‘Abstract, Data collection and analysis' section for clarity.

CONTRIBUTIONS OF AUTHORS

LC and JP designed and wrote the protocol, conducted the search and analyses, and wrote the manuscript for the previous version of this review.

For this update, JP, NM, and LC contributed to the screening of articles and extraction of data. Similarly, JP, NM, and LC contributed to the data interpretation and preparation of GRADE summaries.

JP drafted the final manuscript.

All authors read and approved the final manuscript.

DECLARATIONS OF INTEREST

JP: none.

NM: none.

LC: none.

SOURCES OF SUPPORT

Internal sources

- Liverpool School of Tropical Medicine, UK

External sources

- Foreign, Commonwealth and Development Office (FCDO), UK

  Project number: 300342-104
- World Health Organization (WHO), Switzerland

  WHO Global Malaria Programme Agreement for Performance of Work (APW) Grant 2017 (number 709319)
- Partnership for Increasing the Impact of Vector Control (PIIVeC), UK

  Provided support to LC. PIIVeC is funded by the Medical Research Council of the UK (grant number MR/P027873/1) through the Global Challenges Research Fund.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Differences between protocol and first published version of the revew (Choi 2019):

We amended the title from 'The combination of indoor residual spraying with insecticide-treated nets versus insecticide-treated nets alone for preventing malaria' to 'Indoor residual spraying for preventing malaria in communities using insecticide-treated nets'.

In the protocol, we initially limited the outcome of insecticide resistance to the specific insecticide used for IRS (Choi 2017). However, during the extraction process, it became apparent that resistance to pyrethroid insecticides was also an important outcome in studies using non-pyrethroid-like insecticides for IRS. Therefore, we extracted resistance outcome data for both classes of insecticide.

We also made changes to the way that we subgrouped studies. Initially, we intended to include all comparisons of IRS plus ITNs versus ITNs alone in one analysis, regardless of the target site of the insecticide used for IRS. However, we prespecified that we would subgroup the data by this target site to explore potential causes of heterogeneity. Following referee feedback, it became clear that the most important policy question was to assess the effectiveness of combining ITNs with a non-pyrethroid-like IRS. Therefore, we decided not to conflate this analysis with that of the pyrethroid-like IRS interventions, and instead presented two separate comparisons.

Differences between protocol and this review update:

Prespecified changes to the protocol for this review update received editorial approval on 4 December 2020. A summary of the changes made and justification for the changes are provided in Table 10.

Professor Paul Garner left the review team and Nancy Medley joined the team.

INDEX TERMS

Medical Subject Headings (MeSH)

*Insecticide-Treated Bednets; *Insecticides; *Malaria [prevention & control]; Mosquito Control; Mosquito Vectors; Tanzania

MeSH check words

Adult; Animals; Humans