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The combination of indoor residual spraying with insecticide-treated nets versus insecticide-treated nets alone for preventing malaria (Protocol)

Choi L, Pryce J, Garner P

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The combination of indoor residual spraying with insecticide-treated nets versus insecticide-treated nets alone for preventing malaria.
Cochrane Database of Systematic Reviews 2017, Issue 6. Art. No.: CD012688.
DOI: 10.1002/14651858.CD012688.

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[Intervention Protocol]

The combination of indoor residual spraying with insecticide-treated nets versus insecticide-treated nets alone for preventing malaria

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Editorial group: Cochrane Infectious Diseases Group.
Publication status and date: New, published in Issue 6, 2017.

Citation: Choi L, Pryce J, Garner P. The combination of indoor residual spraying with insecticide-treated nets versus insecticide-treated nets alone for preventing malaria. *Cochrane Database of Systematic Reviews* 2017, Issue 6. Art. No.: CD012688. DOI: 10.1002/14651858.CD012688.

ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To evaluate whether indoor residual spraying (IRS) in combination with long-lasting insecticide-treated nets (LLINs)/insecticide-treated nets (ITNs) causes an additional reduction to malaria transmission versus LLINs/ITNs alone.

BACKGROUND

Description of the condition

Although the number of malaria deaths halved globally between 2000 and 2015, there were 429,000 deaths in 2015 (WHO 2016). It is estimated that 664 million cases have been averted due to malaria control interventions and 79% of this has been attributed to vector control (Bhatt 2015). The 50% reduction of malaria deaths in the past 15 years has been attributed largely to controlling *Anopheles* mosquito species (*Anopheles spp.*) (Bhatt 2015).

Description of the intervention

Vector control depends largely on insecticides: namely in the form of either insecticide-treated nets (ITNs) or indoor residual spraying (IRS) where the insecticide is sprayed indoors on the walls of houses (WHO 2016). ITNs include long-lasting insecticidal nets (LLINs), where the insecticide lasts for up to three years, and nets conventionally treated, where the insecticide is active for up to 12 months. Currently, only pyrethroid class insecticides are deemed safe enough to be used for LLINs/ITNs (Zaim 2000). This restriction is not true for IRS insecticides as humans are less likely to come into contact with the treated surface compared to a net. IRS with dichloro-diphenyl-trichlorethane (DDT) was the main intervention of the malaria eradication programmes in the mid-20th century (Pluess 2010). Malaria was eliminated in many parts of South America, Europe, and Asia and these elimination programmes focused predominantly on IRS (Pluess 2010). Despite the successes of IRS, many countries today choose to adopt LLINs/ITNs rather than IRS. This is due to LLINs/ITNs being logistically easier to implement than IRS.

How the intervention might work

We would expect an incremental effect by having a combination of two vector control interventions, particularly two that both target endophilic and endophagic vectors, rather than one alone. As with many vector control interventions, the reality is not as simple since it involves dealing with both human behaviour and vector behaviour, which will determine the success of the intervention (Killeen 2006). Mosquito exophily can also play a role in the effectiveness of IRS and LLINs/ITNs as mosquitoes that tend to rest outdoors more will have less contact with a treated wall inside a house (Kitau 2012). Earlier biting times of *Anopheles spp.* have been observed, which can reduce the impact of LLINs/ITNs as the mosquitoes are more likely to encounter a human to bite (Ojuka 2015). Modelling data has even suggested an antagonistic effect of combining IRS with LLINs/ITNs when LLIN/ITN coverage is poor (Yakob 2011).

Countries that have deployed both LLINs and IRS are doing so now as a reactive measure because of high pyrethroid resistance in *Anopheles* mosquitoes. However, a combination of LLINs/ITNs with a non-pyrethroid IRS can also be used as a proactive measure, as part of an insecticide resistance management (IRM) strategy to prevent pyrethroid resistance (WHO 2012). Rotating the insecticide used for IRS each year could also form part of an IRM strategy. However, the current World Health Organization (WHO) guidelines for IRM are inadequate in addressing how and when combinations and rotations of IRS with LLINs should be carried out (WHO 2012).

Why it is important to do this review

IRS is logistically more demanding and more expensive than distributing bed nets (Kleinschmidt 2009). For example, an LLIN typically lasts three to five years whereas the residual activity of an insecticide on the wall lasts half a year at best with the current set of insecticides used for IRS (WHO 2015b). Therefore an effective spray campaign in a setting with perennial malaria transmission would require several sprays a year. To add to this, a net distribution campaign can be done at a community health centre, at a village central point, and sometimes house-to-house. In contrast, carrying out IRS must involve visiting every individual household. An IRS programme takes a substantially higher amount of financial commitment than a net distribution campaign (Goodman 2001). Moreover, the sheer quantity of insecticide required per treatment for IRS becomes grossly unaffordable at programmatic scales with most non-pyrethroids even for a single application per year.

There has also been conflicting advice from the WHO. The WHO has recommended combinations of both LLINs/ITNs with IRS in the past but only for epidemic situations, as stated in the Global Technical Strategy (WHO 2015a). This contradicts the advice of the WHO Elimination Framework which recommends that all countries should aim to have the capacity to deploy IRS on top of LLINs/ITNs but that the introduction of IRS should not be used to compensate for poor coverage of LLINs/ITNs (WHO 2017). In the past few years, combining treated nets with IRS has been a contentious issue due to variable results from several randomized controlled trials. As described above, spray campaigns and net distributions are organized differently. Combining the two interventions would be difficult. However, it would be worthwhile if they can achieve a greater impact than LLINs/ITNs alone. This raises the question, in areas where the usage of LLINs/ITNs is common practice, does IRS add additional reduction of malaria transmission?

OBJECTIVES

To evaluate whether indoor residual spraying (IRS) in combination with long-lasting insecticide-treated nets (LLINs)/insecticide-treated nets (ITNs) causes an additional reduction to malaria transmission versus LLINs/ITNs alone.

METHODS

Criteria for considering studies for this review

Types of studies

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

Types of participants

All people living in a rural or urban malarious area, all levels of endemicity including both stable and unstable transmission.

Types of interventions

Intervention

IRS using the World Health Organization (WHO)-recommended dosage (see Table 1) in combination with the control.

Control

LLINs/ITNs with (a) either a full or preliminary recommendation by the WHO or (b) a net treated with insecticide at the WHO-recommended dose (Table 2; Table 3).
Any other malaria intervention(s) that is not IRS must be equal in all treatment arms.

Types of outcome measures

Primary outcomes

To be eligible for inclusion, a study must report at least one of the following primary outcomes.

- Incidence: measured as a count per person unit time of (a) infections or (b) new infections, following treatment to avoid measuring pre-existing infections. Infection is defined as any symptom, including fever, with confirmed parasitaemia (by blood smear microscopy or rapid diagnostic test (RDT)).
- Parasite prevalence: the proportion of surveyed individuals with confirmed parasitaemia.

Secondary outcomes

Entomological

- Entomological Inoculation Rate (EIR): the estimated number of bites by infectious mosquitoes per person per unit time. This is measured using the human biting rate (the number of mosquitoes biting an individual 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.
- Adult mosquito density: measured by a technique previously shown to be appropriate for the vector (measured using human baits, light traps, knock-down catches, baited huts, or other methods).
- Sporozoite rate.

Epidemiological

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

Unwanted outcome

- An increase in the level of insecticide resistance respective of the class of insecticide used for IRS confirmed by WHO cylinder assays/Centers for Disease Control and Prevention (CDC) bottle bioassays/molecular techniques. This is an unwanted outcome of trials due to increased coverage of insecticidal interventions.

Search methods for identification of studies

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

Electronic searches

We will search the following databases using the search terms and strategy described in Appendix 1: Cochrane Infectious Diseases Group Specialized Register; Central Register of Controlled Trials (CENTRAL), published in the Cochrane Library; MEDLINE (PubMed); Embase (OVID); and LILACS, using the search terms detailed in Appendix 1. We will also check the WHO International Clinical Trials Registry Platform (WHO ICTRP; http://www.who.int/ictrp/en/) and ClinicalTrials.gov (https://clinicaltrials.gov/ct2/home) for ongoing trials using the terms: indoor residual spraying; IRS; insecticide-treated nets; bednets; ITNs; LLIN.

Searching other resources

We will contact researchers working in the field for unpublished data. We will also check the citations of all trials identified by the above methods.

Data collection and analysis

Selection of studies

Two review authors (LC and JP) will independently assess the titles and abstracts of trials identified by the searches. The same two review authors will assess full-text copies of potentially relevant trials for inclusion using an eligibility form based on inclusion criteria. We will compare the results of our assessments and will resolve any disagreements by discussion and consensus, with arbitration

by a third review author (PG) if necessary. We will ensure that multiple publications of the same trial are included once. We will list excluded studies, together with their reasons for exclusion, in a 'Characteristics of excluded studies' table. We will illustrate the study selection process in a PRISMA diagram.

Data extraction and management

Two review authors (LC and JP) will independently extract information from the trials using pre-piloted, electronic data extraction forms. In case of differences in extracted data, the two review authors will discuss these differences to reach consensus. If unresolved, we will consult a third review author (PG). In case of missing data, we will contact the original study author(s) for clarification.

We will extract data on the following.

- Trial design: type of trial; method of participant selection; adjustment for clustering (for cluster-RCTs (cRCTs)); sample size; method of blinding of participants and personnel.
- Participants: trial settings and population characteristics; recruitment rates; withdrawal and loss to follow-up.
- Intervention: description of intervention and control (active ingredient, dose, formulation, method, frequency and timing of application, buffer zone between clusters); co-interventions; description of control; coverage of intervention, control, and co-interventions; compliance of intervention, control, and any co-interventions.
- 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, exo/endophilic, exo/endophagic, anthro/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 whilst the trial was running); genotypic insecticide resistance profile (either performed during the trial or if the trial references data from previous studies done on the same local vector population within the previous five years);
    - malaria endemicity; eco-epidemiological setting; population proximity and density; *Plasmodium* species.

For dichotomous outcomes, we will extract the number of patients experiencing each outcome and the number of patients in each treatment group. For count/rate data outcomes, we will extract the number of outcomes in the treatment and control groups, and the total person time at risk in each group or the rate ratio, and a measure of variance (for example, standard error). For continuous outcomes, we will extract the mean and a measure of variance (standard deviation).

For cRCTs we will record the number of clusters randomized; number of clusters analysed; measure of effect (such as risk ratio, odds ratio, or mean difference) with confidence intervals (CI) or standard deviations; number of participants; and the intracluster correlation coefficient (ICC) value.

For non-randomized studies, we will extract adjusted measures of intervention effects that attempt to control for confounding.

Assessment of risk of bias in included studies

Two review authors (LC and JP) will independently assess 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 cluster-randomized trials (Higgins 2011a; Higgins 2011b). We will assess non-randomized controlled trials and ITS trials for risk of bias using Cochrane EPOC's 'Risk of bias' tool. We will resolve any discrepancies through discussion or by consulting a third review author (PG). We will classify judgements of risk of bias as either at low, high, or unclear risk of bias, and we will use summary graphs ('Risk of bias' summary and 'Risk of bias' graph) to display results.

Measures of treatment effect

We will compare intervention and control data using risk ratios and for count/rate data, rate ratios. We will use adjusted measures of effect to summarize treatment effect from non-randomized studies. We will present all results with their associated 95% CIs.

Unit of analysis issues

For cRCTs, or cluster non-randomized trials, we will extract adjusted measures of effect where possible. If the study authors did not perform any adjustment for clustering, we will adjust the raw data ourselves using an ICC value. If an ICC is not reported in the paper, we will obtain this from similar studies, or estimate the ICC value. We will not present results from cluster-randomized trials that are not adjusted for clustering. If we estimate the ICC, we will perform sensitivity analyses to investigate the robustness of our analyses.

If we identify studies for inclusion that have multiple intervention arms, we will include data from these studies by either combining treatment arms, or by splitting the control group so that we only include these participants in the meta-analysis once.

Dealing with missing data

In case of missing data, we will apply available-case analysis, only including data on the known results. The denominator will be

the total number of participants who had data recorded for the specific outcome. For outcomes with no missing data, we plan to perform analyses on an intention-to-treat basis. We will include all participants randomized to each group in the analyses and will analyse participants in the group to which they were randomized.

Assessment of heterogeneity

We will inspect forest plots for overlapping CIs and will assess statistical heterogeneity in each meta-analysis using the I^2 statistic values and Chi^2 statistics. We will regard heterogeneity as moderate if I^2 statistic values are between 30% to 60%; substantial if they are between 59% to 90%; and considerable if they are between 75% to 100%. We will regard a Chi^2 test statistic with a P value ≤ 0.10 indicative of statistically significant heterogeneity. We will explore clinical and methodological heterogeneity through consideration of the trial populations, methods, and interventions, and by visualization of trial results.

Assessment of reporting biases

If there are 10 or more trials included in each meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually, and use formal tests for funnel plot asymmetry (Harbord 2006). If we detect asymmetry in any of these tests or by a visual assessment, we will explore the reasons for asymmetry.

Data synthesis

We will analyse data using Review Manager 5 (RevMan 5) (RevMan 2014). We will use fixed-effect meta-analysis to combine data if heterogeneity is absent. If considerable heterogeneity is present, we will combine data using random-effects meta-analysis and report an average treatment effect. We will decide whether to use fixed-effect or random-effects models based on the consideration of clinical and methodological heterogeneity between trials, as described previously.

Certainty of the evidence

We will assess the certainty of the evidence using the GRADE approach (Guyatt 2011). We will rate each primary 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 start as high quality evidence but can be downgraded if there are valid reasons within the following five categories: risk of bias, imprecision, inconsistency, indirectness, and publication bias. Studies can also be upgraded if there is 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 no effect was observed (Balshem 2011). We will summarize our findings in a 'Summary of findings' table.

Subgroup analysis and investigation of heterogeneity

We will explore reasons for substantial heterogeneity using subgroup analysis. We plan to perform the following subgroup analyses.

- Use of LLINs/ITNs defined by individual use from the previous night:
  - high (80% to 100%);
  - moderate (50% to 79%);
  - low (less than 50%).
- Coverage of IRS:
  - high (80% to 100%);
  - moderate (50% to 79%);
  - low (less than 50%).
- Seasonality of malaria:
  - perennial;
  - seasonal;
  - epidemic.
- Mode of action of insecticides used for IRS:
  - voltage-gated sodium ion channels;
  - acetylcholinesterase.

We will assess differences between subgroups using the Chi^2 test, with a P value less than 0.05 indicating statistically significant differences between subgroups.

Sensitivity analysis

We will perform sensitivity analysis on the primary outcome to see the effect of exclusion of trials at high risk of bias (for allocation concealment and incomplete outcome data) on the overall results. If the ICC value is estimated, we will undertake sensitivity analyses to investigate the impact of varying the ICC value on meta-analysis results.

ACKNOWLEDGEMENTS

We are grateful to Vittoria Lutje, Information Specialist with the Cochrane Infectious Diseases Group (CIDG), for help with the literature search strategy.

Leslie Choi, Joseph Pryce, and Paul Garner are supported by the Effective Health Care Research Consortium. This Consortium and the CIDG editorial base are funded by UK aid from the UK Government for the benefit of developing countries (Grant: 5242). The views expressed in this review do not necessarily reflect UK government policy.

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* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. WHO-recommended insecticides for IRS against malaria vectors

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

Table 1. WHO-recommended insecticides for IRS against malaria vectors (*Continued*)

Lambda-cyhalothrin WP, CS	0.02 to 0.03

Abbreviations: CS: capsule suspension; DDT: dichloro-diphenyl-trichlorethane; EC: emulsifiable concentrate; IRS: indoor residual spraying; SC: suspension concentrate; SC-PE: polymer-enhanced suspension concentrate; WHO: World Health Organization; 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. WHO-recommended LLINs

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

Abbreviations: LLIN: long-lasting insecticidal nets; WHO: World Health Organization.

Table 3. WHO-recommended insecticide products for treatment of mosquito nets for malaria vector control

Insecticide	Formulation	Dosage (mg AI/m² of netting)
Alpha-cypermethrin	SC 10%	20 to 40
Cyfluthrin	EW 5%	50
Deltamethrin	SC 1%; WT 25%; and WT 25% + binder	15 to 25
Etofenprox	EW 10%	200
Lambda-cyhalothrin	CS 2.5%	10 to 15
Permethrin	EC 10%	200 to 500
ICON MAXX (long-lasting lambda-cyhalothrin formulation)	CS 10% + binder	50 to 83

Abbreviations: AI: active ingredient; EC: emulsifiable concentrate; EW: emulsion, oil in water; CS: capsule suspension; SC: suspension concentrate; WT: water dispersible tablet; WHO: World Health Organization.

APPENDICES

Appendix 1. Search strategy

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

(*Continued*)

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]
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

This is the preliminary search strategy for MEDLINE (Pubmed). It will be adapted for other electronic databases. We will report all search strategies in full in the final version of the review.

CONTRIBUTIONS OF AUTHORS

All protocol authors contributed to the protocol design, writing the protocol, and approved the final version.

DECLARATIONS OF INTEREST

LC has no known conflicts of interest to declare.

JP has no known conflicts of interest to declare.

PG is the Director of the Effective Health Care Research Consortium, a DFID-funded research programme that aims to increase the number of decisions in low- and middle-income countries based on reliable evidence.

SOURCES OF SUPPORT

Internal sources

- Liverpool School of Tropical Medicine, UK.

External sources

- Department for International Development, UK.

Grant: 5242

- World Health Organization (WHO), Switzerland.

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