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[Intervention Protocol]

Indoor residual spraying for preventing malaria

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ABSTRACT

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

To evaluate the impact of indoor residual spraying (IRS) on malaria disease burden.

BACKGROUND

Description of the condition

Malaria is a parasitic disease caused by a number of *Plasmodium* species, and is transmitted by the bite of female mosquitoes from several *Anopheles* species (WHO 2018a). *Plasmodium falciparum* and *Plasmodium vivax* are the most prevalent parasite species; *P falciparum* is responsible for the most deaths. Despite decades of control activities, malaria continues to cause more deaths than any other parasitic disease worldwide, and it impedes socioeconomic development. Annual incidence has declined since 2010; however, in more recent years progress in malaria control has stalled, with no significant reduction in malaria cases observed between 2015 to 2017. Over 219 million cases and 435,000 malaria-related deaths are estimated to have occurred globally in 2017, and approximately half of the global population is believed to be at risk of malaria (WHO 2018a). This burden is disproportionately distributed; almost 80% of malaria cases occur in 15 sub-Saharan African countries and India, and 93% of deaths from malaria occur in Africa. Individuals most at risk of dying from malaria are those with low levels of immunity, reduced access to healthcare services, and those who are highly exposed to infectious bites. Globally, major barriers to achieving malaria control and elimination include the emergence of *Plasmodium* resistance to antimalarial medications; *Anopheles* resistance to insecticides; conflict, which limits the delivery of healthcare services in endemic regions; inadequate funding; and lack of an effective vaccine (Alonso 2013).

Description of the intervention

Indoor residual spraying (IRS) involves the application of insecticide products to the interior surfaces (walls and ceilings) of households, public buildings, or animal dwellings in areas where individuals are considered at risk of malaria (or other vector-borne diseases, including Chagas disease and leishmaniasis). It is most effective against endophilic (indoor-resting), endophagic (indoor-biting) mosquitoes from the *Anopheles* species that rest on these surfaces. The vector control group of the World Health Organization (WHO) Prequalification Team recommends numerous insecticidal chemicals for use in IRS, such as organophosphates, carbamates, pyrethroids, and dichlorodiphenyltrichloroethane (DDT;

the only organochlorine that is solely recommended when no affordable alternative is available). Clothianidin (a neonicotinoid insecticide) has recently been added to this list, and an interim recommendation has been made for chlorfenapyr, an insecticide belonging to a class known as halogenated pyrroles (WHO 2015; WHO 2018b). Depending on the conditions in the given setting (for example, seasonality of transmission, and duration of effective action of the insecticide being utilized), IRS needs to be repeated every three to nine months in targeted areas, over large geographical areas, or applied in areas identified as malaria hotspots. It may be undertaken as a preventative measure or in response to cases being detected.

Indoor residual spraying has been widely used in malaria control programmes worldwide since the 1940s. The success of the Global Malaria Eradication Campaign (GMEP) between 1955 and 1969 has been largely attributed to large-scale DDT-IRS campaigns (Najera 2011).

Following the introduction of IRS with DDT under national malaria control programmes implemented during the 1940s, 1950s, and 1960s, malaria was eliminated in many regions, and sharp declines in infection and vector densities were reported in other areas, such as Southern Africa and India (Mabaso 2004). While IRS remains a core malaria control activity in several countries worldwide, including regions of South America and India, population coverage has declined on both regional and global scales since 2010, as insecticide-treated net (ITN) coverage has increased (WHO 2018a). Additional factors which have contributed to the reduced use of IRS include lack of government commitment to funding IRS programmes, and concerns regarding community acceptance and the selection of insecticide resistance (WHO 2006a).

How the intervention might work

Most female *Anopheles* mosquitoes are endophagic, endophilic, and night-biting. Indoor residual spraying exploits these behaviours, and protects individuals from malaria transmission, through targeting and killing mosquitoes that rest on a wall after blood feeding (WHO 2015). This aims to reduce abundance and shorten the average mosquito's lifespan to less than the time necessary for *Plasmodium* to undergo its lifecycle in the vector. In contrast to topical repellents and mosquito nets, which provide personal protection and prevent biting from occurring, IRS operates largely at a community level and targets vectors that have already taken a blood meal. High coverage (usually more than 85% of all potential indoor resting sites) therefore needs to be achieved for IRS to be effective.

Due to financial and logistical implications, the WHO recommends that IRS be prioritized only in regions that experience a single annual peak in malaria transmission and have densely spaced housing, or where a rapid decline in vector density needs to be achieved, for example during an outbreak (WHO 2015). Other interventions, particularly ITNs, are alternatively recommended for contexts where long-term vector control needs to be sustained (WHO 2006b).

Why it is important to do this review

Following the discovery of DDT in the 1940s, IRS became popularized and its success in various pilot projects across the world ultimately inspired the initiation of the GMEP, with IRS featured as a core component (Nájera 1999). This happened at a time where high-quality evidence was not a prerequisite for vector control policy recommendations, and the subsequent success of the GMEP programme in many parts of the world meant that the efficacy of IRS as a malaria control intervention was widely accepted. For this reason, only a limited number of studies using strong experimental designs have been conducted.

A Cochrane Review evaluating IRS, Pluess 2010, was restricted to randomized controlled trials (RCTs) with three units per study arm, controlled before-and-after studies (CBAs), and interrupted time series (ITS) analyses. Six studies met the inclusion criteria and the results on the effect of IRS in different transmission settings were inconclusive. There has been repeated criticism of the review because observational studies were excluded, despite the substantial evidence base for IRS that was generated prior to the widespread adoption of experimental designs for community malaria interventions (WHO 2017). For this new Cochrane Review, we will include prospective cohort studies, quasi-experimental randomized studies, and RCTs with two units per study arm, in addition to RCTs with three units per study arm, CBAs, and ITS studies.

It remains unclear whether there are significant additional benefits of adding IRS to ITNs, and this is a question that will be addressed in a separate Cochrane review (Choi 2017). In order to minimize the risk of diluting or overestimating the effect of IRS alone on malaria transmission, we have therefore chosen to exclude studies where there is thought to be moderate to high coverage of ITNs. For this reason, we will exclude all studies conducted after 2003 due to the known widespread coverage of ITNs in Africa at this time, and increases in ITN coverage globally from 2003 onwards (Bhatt 2015; Noor 2009).

OBJECTIVES

To evaluate the impact of indoor residual spraying (IRS) on malaria disease burden.

METHODS

Criteria for considering studies for this review

Types of studies

Cluster-randomized controlled trials (cRCTs) with:

- baseline data;
- monitoring of at least one transmission season; and
- at least two clusters per arm.

Quasi-experimental designs including stepped wedge where sites are randomly allocated.

Interrupted time series (ITS) designs with:

- a clearly defined point in time when the intervention occurred; and
- at least three data points before, and three after, the intervention.

Randomized cross-over studies and non-randomized cross-over studies with:

- a clearly defined point in time when the cross-over occurred; and
- monitoring of at least two transmission seasons before and after the cross-over.

Controlled before-and-after studies (CBAs) with:

- a contemporaneous control group; and
- monitoring of at least one transmission season before and after the intervention; and at least two sites per study arm.

Prospective cohort studies with:

- baseline data and exclusion of existing cases to ensure exposure preceded outcome; and
- monitoring of at least two transmission seasons following baseline data collection.

Types of participants

Individuals of all age groups living in areas where malaria transmission occurs.

Types of interventions

Intervention

Indoor residual spraying (IRS) using the insecticides recommended by the WHO, at the appropriate target dosage (Table 1).

Control

- No other insecticidal malaria vector control interventions; or
- IRS using an alternative regimen, including IRS sprayed at an alternative point in time or alternative frequency.

Any other interventions for malaria control, such as mass drug administration and untreated mosquito nets, must be delivered in both the intervention and control arms, at the same level of delivery.

Due to the known widespread coverage of ITNs in Africa, and increases in ITN coverage globally from 2003 onwards, we will exclude all studies conducted after 2003 from the review (Noor 2009).

Types of outcome measures

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

Primary outcomes

- Malaria case incidence: measured as number of cases per unit of time or the number of new uncomplicated malaria cases. We will use site-specific definitions as long as they have demonstrated: a) a fever or history of fever, and b) confirmed parasitaemia (by blood smear microscopy, rapid diagnostic test or PCR).
- Incidence of new malaria infection: measured as count per person unit time or the number of new infections.
- Parasite prevalence: the proportion of surveyed individuals with confirmed parasitaemia at a community household survey.

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 (e.g. human baits, light traps, knock-down catches, baited huts, or other methods).
- Sporozoite rate: measured as the number of caught adult mosquitoes positive for malaria sporozoites. Sporozoites can be detected through molecular or immunological methods.

Epidemiological

- Anaemia prevalence: defined according to WHO cut-offs based on haemoglobin measurements taken in community household surveys (Table 2; WHO 2011).

Adverse effects

- Any indicators of adverse effects of the intervention, including the following, will be reported in the review:
  - Reports of poisoning in humans due to increased exposure to insecticides
  - Environmental impacts, such as changes to the biodiversity and ecosystem due to the addition of insecticides.
  - An increase in the level of phenotypic/molecular 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.
  - Changes in mosquito behaviour that reduce the efficacy of vector control interventions, for example an increase in exophily, exophagy, zoophily, or changes in biting time.

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 (CIDG) Specialized Register; Central Register of Controlled Trials (CENTRAL), published in the Cochrane Library; MEDLINE (Pubmed); Embase (OVID); Armed Forces Pesticide Management Board (AFPMB); CAB Abstracts (Web of Science); and LILACS . We will also search the WHO International Clinical Trials Registry Platform (who.int/ictrp/search/en//), ClinicalTrials.gov, and the ISRCTN registry (isrctn.com/) to identify ongoing trials, using "malaria", "anopheles", "indoor residual spraying", "IRS", and "house spraying" as search terms.

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 (JFA and SM) will independently assess the titles and abstracts of studies identified by the searches. The same two review authors will assess full-text copies of potentially relevant studies for inclusion, using an eligibility form based on the 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 (LC) if necessary. We will ensure that multiple publications of the same study 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 (Moher 2009).

We anticipate that primary studies evaluating IRS were carried out at scale in large programmes with operational before-and-after comparisons, some of which were probably very important in the acceptance and adoption of the use of IRS for preventing malaria. Whilst these studies will be excluded based on our inclusion criteria, we will identify those CBA studies with at least one site per study arm and summarize these in an additional analysis of programme implementation in a review annex.

Data extraction and management

Two review authors (JFA and SM) will independently extract information from the studies 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 (LC). 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 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 (active ingredient, dose, formulation, frequency and timing of application, buffer zone between clusters); coverage and adherence of the intervention; any reports of people refusing the intervention and their reasons behind these decisions.
- Details of cointerventions (for example, mass drug administration; untreated bednets; active case detection; or health education); information on coverage and adherence; any reports of people refusing the intervention and their reasons behind these decisions.
- 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 (population stability, adult habitat, peak biting times, exophilic/endophilic, exophagic/endophagic, anthropophilic/zoophilic); method of mosquito collection(s); baseline measures of phenotypic insecticide resistance and any measures during the

study period (based on WHO definitions if supplementary WHO cylinder assays or CDC bottle bioassays or LD50s or LD95s (lethal dose required to kill 50% or 95% of mosquitoes, respectively) from larval or adult dose response assays); baseline measures of genotypic insecticide resistance profile and any measures during the study period; 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 (CIs) 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. If no adjusted measures are reported, we will extract unadjusted measures.

Assessment of risk of bias in included studies

Two review authors (JFA and SM) will independently assess the risk of bias. For each included cRCT, we will use the Cochrane 'Risk of bias' tool, as well as 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 will assess non-randomized controlled trials and ITS trials using the 'Risk of bias' tool from the Cochrane Effective Practice and Organisation of Care (EPOC) Group (EPOC 2017). We will classify judgements of risk of bias as either at low, high, or unclear risk of bias, and we will use summary graphs to display results.

For observational studies, we will use the Cochrane Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool (Sterne 2016). We will assess risk of bias through a hierarchy of domains, starting with critical then serious, moderate, and low. If any domain reaches critical risk of bias we will not continue with the assessment, as further evaluation will not influence how we assess the certainty of the evidence. As the risk of bias in the effect of an intervention may be different for different outcomes, we will make a 'Risk of bias' assessment for each outcome. The confounding domains are outlined in Appendix 2.

The ROBINS-I tool recommends only including non-randomized studies that are not classified as having critical risk of bias. For our main effects analysis, we will follow this approach. As a secondary analysis, we will perform an analysis of data including studies with a critical risk of bias to provide an assessment of the degree to which different confounding variables may influence effect estimates. We expect that some studies that have traditionally been used as part of the evidence base will meet the inclusion criteria, but will be judged as having critical risk of bias according to ROBINS-I. We will therefore carry out a subsidiary descriptive analysis for all studies that are considered to be at critical risk of bias and report their estimates of effect. We will perform sensitivity analysis for these studies to describe the effect of confounding.

We will resolve any discrepancies through discussion or by consulting a third review author (LC).

Measures of treatment effect

We will compare intervention and control data using risk ratios or odds ratios. For count/rate data, we will use rate ratios; for continuous data, we will use the mean difference. We expect incidence to be reported as either a rate ratio or risk ratio and for prevalence to be reported as a risk ratio or odds ratio. 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 non-randomized cluster 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 and Chi^2 statistics. We will regard heterogeneity as: moderate if I^2 statistic values are between 30% and 60%; substantial if they are between 50% and 90%; and considerable if they are between 75% and 100% (Higgins 2011c). We will regard a Chi^2 test statistic with a P value of 0.10 or less as 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 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. We will stratify the analysis by study design. Any studies conducted in epidemic settings will be considered in a separate analysis.

Certainty of the evidence

We will assess the certainty of the evidence using the GRADE approach (Guyatt 2011). We will rate each primary outcome for RCTs, as described in Balshem 2011.

For non-randomized studies, we will used GRADE to rate primary outcomes where there is a low risk of bias from the ROBINS-I tool. For these studies, we will start with a rating of high certainty, and downgrade or upgrade our assessment from that point. Where the following outcome domains are judged to have moderate, high, or unclear risk of bias, we will begin with a rating of low certainty of evidence.

- Bias due to confounding.
- Bias due to missing data.
- Bias in selection of the reported result.

We will use the following definitions to assess the certainty of the evidence.

- 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.

Randomized controlled trials 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.

Non-randomized studies can be upgraded (provided they are not downgraded for any reason) 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.

- Coverage of IRS:
    - high (80% to 100%);
    - moderate (50% to 79%); or
    - low (less than 50%).

We expect that the coverage of IRS would be an effect modifier when looking at the efficacy from a community level. Previous studies have suggested that there is no benefit associated with low coverage IRS (less than 20%), whereas in areas of high coverage (greater than 80%), community-wide benefits can be observed (Larsen 2017).

- Transmission pattern:
    - stable (characterized by a steady prevalence pattern, with little variation from one year to another); or
    - seasonal (transmission that occurs only during some months of the year and is markedly reduced during other months) or unstable (epidemic).

In areas of unstable or seasonal malaria transmission, the timing and frequency of IRS will likely affect its efficacy (Worrall 2007). Therefore, IRS may be more efficacious in areas of stable transmission, where IRS is less dependent on the timing and frequency of spraying.

- Resistance to insecticide used for IRS in the study (data for this can be from within five years of the study period):
    - present;

- absent; or
- no data.

Resistance to various classes of insecticide has been reported since dichlorodiphenyltrichloroethane (DDT) was first introduced, and there is increasing evidence that insecticide resistance is associated with negative epidemiological outcomes (Ranson 2011; Protopopoff 2018). Therefore, IRS is likely to be less effective in areas where there are high levels of resistance.

- Population mobility:
  - migrant or displaced populations, including refugees, migrant workers and nomadic people; or
  - non-migrant populations.

We expect that IRS will be more effective in non-migrant populations where individuals are more likely to be consistently spending time in insecticide-sprayed houses.

Sensitivity analysis

We will perform sensitivity analysis on the primary outcomes, to observe the effect of excluding trials at high risk of bias with regards to incomplete outcome data. If the ICC value is estimated, we will undertake sensitivity analyses to investigate the impact of varying the ICC value on meta-analysis results.

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* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. WHO-recommended insecticides for indoor residual spraying 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
Lambda-cyhalothrin WP, CS	0.02 to 0.03

Table 1. WHO-recommended insecticides for indoor residual spraying against malaria vectors (*Continued*)

SumiShield WG	0,03

Chlorfenapyr 240 SC: the current assessments of Chlorfenapyr SC (class group: pyrrole) are available in the report of the 16th WHOPES Working Group meeting, 22-30 July 2013, and the report of the 17th WHOPES Working Group meeting, 15-19 September 2014 (WHO 2013; WHO 2014). Table modified from WHO 2018c.

Abbreviations: AI: active ingredient 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. Haemoglobin levels used to diagnose anaemia (WHO 2011)

Population	Non-anaemia[a]	Anaemia[a]		
		Mild	Moderate	Severe
Children 6 to 59 months of age	110 or higher	100 to 109	70 to 99	< 70
Children 5 to 11 years of age	115 or higher	110 to 114	80 to 109	< 80
Children 12 to 14 years of age	120 or higher	110 to 119	80 to 109	< 80
Non-pregnant women (15 years of age and above)	120 or higher	110 to 119	80 to 109	< 80
Pregnant women	110 or higher	100 to 109	70 to 99	< 70
Men (15 years of age and above)	130 or higher	110 to 129	80 to 109	< 80

[a] Haemoglobin in g/L.

APPENDICES

Appendix 1. MEDLINE search strategy

Search set	Search terms
1	Malaria* Title/Abstract , [Mesh]
2	Anopheles Title/Abstract , [Mesh]
3	1 or 2
4	"indoor residual spray*" or IRS Title/Abstract
5	"house spraying" or "house spray" Title/Abstract
6	"Pyrethrins/administration and dosage"[Mesh]
7	"Mosquito Control/instrumentation"[Mesh] OR "Mosquito Control/methods"[Mesh])
8	("Insecticides/instrumentation"[Mesh] OR "Insecticides/therapeutic use"[Mesh])
9	4 or 5or 6 or 7
10	3 and 9
11	"Randomized Controlled Trial" [Publication Type] OR "Controlled Clinical Trial" [Publication Type]
12	randomized or placebo or randomly or trial or groups Title/Abstract
13	drug therapy [sh]
14	"Interrupted Time Series Analysis"[Mesh]
15	"Controlled Before-After Studies"[Mesh
16	"time series" Title/Abstract
17	"cross-over studies"[MeSH] or crossover or cross-over Title/Abstract
18	"longitudinal studies"[MeSH]
19	Longitudinal or cohort* Title/Abstract
20	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21	10 and 20

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 review version.

Appendix 2. Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool: protocol stage

ROBINS-I tool (Stage I): protocol stage

Specify the review question

Participants	Anyone living in an area with malaria.
Experimental intervention	IRS using the World Health Organization (WHO)-recommended dosage (WHO 2015).
Comparator	No other insecticidal malaria vector control. Any other interventions for malaria control will have to be balanced in all study arms
Outcomes	Malaria case incidence, incidence of new malaria infections, malaria parasite prevalence

List the confounding domains relevant to all or most studies

- Socioeconomic status: those of lower socioeconomic status may be less likely to live in homes with walls appropriate for IRS and therefore less likely to be selected for the intervention group. Socioeconomic status is considered a prognostic factor for malaria (Somi 2007).

- Geographical location: those living in certain geographic regions may live in houses that are more appropriate or more convenient for IRS spraying and therefore may be more likely to be selected for the intervention group. For example, houses that are better connected to roads might be more convenient to spray. Malaria transmission is also heterogenous across different geographical regions and can therefore be a predictor of malaria risk (Bousema 2012).

- Population mobility: more mobile populations may be less likely to be chosen for studies due to inconveniences associated with measuring clinical outcomes. Population movement is also a risk factor for malaria; therefore those individuals chosen for the intervention arm may be at lower risk of malaria (Martens 2000).

List cointerventions that could be different between intervention groups and that could impact on outcomes

- Use of other (non-insecticidal) vector control tools: individuals receiving the intervention may feel less inclined to use other vector control interventions such as bed nets.

CONTRIBUTIONS OF AUTHORS

LC, SM, and JFA contributed equally to this work and approved the final version.

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LC has no known conflicts of interest.

SM has no known conflicts of interest.

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