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[Intervention Protocol]

Volatile pyrethroid spatial repellents for malaria prevention

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ABSTRACT

Objectives

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

To assess the effectiveness of volatile pyrethroid spatial repellents (VPSRs) for preventing new cases of *Plasmodium falciparum* and *Plasmodium vivax* malaria.

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BACKGROUND

Description of the condition

Malaria is a deadly and debilitating disease, causing 241 million reported cases and 627,000 deaths in 2020 (WHO 2021). Endemic to 85 countries, malaria is caused by *Plasmodium* parasites, and is transmitted by female *Anopheles* mosquito vectors to humans. There are four *Plasmodium* parasite species that can cause malaria in humans: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, and *Plasmodium malariae* (Greenwood 2005). Additionally, *Plasmodium knowlesi*, a species of simian malaria that can also infect humans, is increasingly responsible for malarial illness in Southeast Asian forest fringe settings (Vythilingam 2013).

Malaria is preventable and treatable. Symptoms include fever, chills, headache, and vomiting, which usually present between 7 and 18 days after the bite of an infected female *Anopheles* mosquito. If not treated rapidly, malaria can disrupt blood supply to vital organs, and become life-threatening. Clinical diagnosis is made using microscopy or a conventional malaria rapid diagnostic test (mRDT); both with detection limits of approximately 100 to 200 parasites/mL (Mwesigwa 2019). For prevalence surveys and research, polymerase chain reaction (PCR) methods offer higher sensitivity levels of 0.002 to 30 parasites/mL, but require laboratory processing (Alemayehu 2013).

The most widely deployed malaria control interventions include mRDTs for diagnosis, artemisinin-based combination therapies for treatment, and the use of insecticide-treated nets (ITNs) for vector control (Bhatt 2015; Feachem 2019). Indoor residual spraying (IRS) is also a highly effective form of vector control, although deployment is much lower than ITN distribution due to high implementation costs (Tangena 2020). These interventions have enabled tremendous progress in the global fight against malaria (Bhatt 2015), which between 2000 and 2015 achieved a 60% reduction in mortality rates and a 37% reduction in case incidence (Cibulskis 2016); however, progress has since stalled (WHO 2021).

Additional approaches and interventions are required to make further progress in reducing malaria transmission globally (Feachem 2019). ITNs only provide protection when people are sleeping indoors, and neither ITNs nor IRS are able to protect people when they are outdoors, or if they do not have permanent homes. Therefore, interventions that can target gaps in protection, such as outdoor transmission as well as amongst mobile/migrant populations are highly desirable (Feachem 2019; Sherrard-Smith 2019). These interventions must also be suitable for high rates of uptake, ideally being simple to use and offering long durations of protection (Feachem 2019). Furthermore, deployment needs to be easy, for limited coverage in distribution has proven to be a challenge for both ITNs (Bertozzi-Villa 2021), and IRS (Tangena 2020).

Experts argue that the use of insecticide-treated clothing, skin repellents, and spatial repellents for personal protection against mosquito bites could be important for reducing malaria transmission missed by ITNs and IRS (Carnevale 2021). While these products have long been available for personal and household use, their application in public health efforts is currently limited. Further evidence on their effectiveness for mosquito bite and disease prevention is required (WHO 2021).

Description of the intervention

Spatial repellents are products that are hung up or placed in a space to diffuse airborne concentrations of an active ingredient, creating a bubble of protection that disrupts mosquito behaviours, thus reducing their contact with humans (Achee 2012). Several forms of spatial repellents are available and in development. Many require energy to vaporize active ingredients. The most widely available of these is the mosquito coil (Zhang 2010), which relies on ignition to combust the coil and disperse active ingredients through convection. Coils rely on daily activation, posing operational requirements for end users (Monroe 2021). Passive emanator spatial repellents (also called ambient emanators), consist of a surface or matrix dosed with an active ingredient that can volatilize under ambient conditions, without heat or electricity. In addition to being usable in settings without electricity, these spatial repellents are designed to last for several weeks without the need for daily user compliance, increasing their ease of use.

How the intervention might work

The World Health Organization (WHO) defines spatial repellency as a range of insect behaviours induced by airborne chemicals that result in a reduction in human–vector contact, providing personal protection to spatial repellent users. These behaviours can include movement away from a chemical stimulus (taxis, avoidance), interference with host detection (attraction inhibition) and feeding response (feeding inhibition) (WHO 2013). Spatial repellent products are usually placed in a space to create a bubble of protection from mosquito bites to all users within that space, and are different from topical repellents which require the active ingredient to be applied directly to the skin of an individual.

Mosquito repellents have traditionally been considered to cause oriented movements away from a host. The term 'spatial repellent' is misleading because these have multiple modes of action not limited to direct taxis or avoidance. Most spatial repellents that are commercially available or in development use volatile pyrethroids as their active ingredients, which are known not only to cause true repellency but also cause additional modes of action, including feeding inhibition, insecticidal activity and disarming (Tambwe 2022), depending on the dose used (Bibbs 2017). Feeding inhibition is defined as the inability of adult female mosquitoes to complete the sequence of behaviours that result in a blood meal, due to inhibition or excitation of olfactory receptor neurons (Sparks 2015), consequently reducing human-vector contact. Insecticidal activity or toxicity results in death of mosquitoes before biting (pre-prandial mortality) or after biting (post-prandial mortality), protecting both users and non-users within a community (Denz 2021; ten Bosch 2019). Disarming entails sublethal incapacitation (knock-down), or prolonged disruption of mosquito odour receptor neurons such that they are unable to host-seek for several hours, protecting users and non-users within a community (Denz 2021). Therefore, if volatile pyrethroid spatial repellents (VPSRs) are applied at scale, these could not only provide personal protection from vector-borne disease but could offer community-level protection by reducing the size and age of the mosquito population.

Why it is important to do this review

In 2017, the World Health Assembly endorsed the Global vector control response 2017-2030, adopting a resolution to promote integrated vector management using effective, locally adapted

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vector control strategies (WHO 2019). This approach encourages the use of vector control tools beyond ITNs and IRS that have demonstrated public health benefit, with particular focus on the development of spatial repellents and vapour active insecticides as innovations that could further reduce disease burden.

VPSRs have long been available for household use, and are now being considered for public health applications. Currently, no VPSRs have a WHO recommendation due to a lack of epidemiological evidence on their efficacy for preventing malaria (WHO 2017). A Cochrane Review published in 2018 titled '*Mosquito repellents for malaria prevention*' found only two studies on spatial repellents to prevent malaria, both of which were VPSRs (Maia 2018). This evidence was deemed insufficient to conclude that spatial repellents could prevent malaria (Maia 2018). However, the evidence base has grown and several randomised controlled trials (RCTs) on VSPRs have since been completed. This review will update the VPSR component of Maia 2018, for which the 2021 *WHO Guidelines for Malaria* stated a need for more studies assessing malaria epidemiological outcomes before a recommendation on their deployment can be made (WHO 2022).

OBJECTIVES

To assess the effectiveness of volatile pyrethroid spatial repellents (VPSRs) for preventing new cases of *Plasmodium falciparum* and *Plasmodium vivax* malaria.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) and cluster-RCTs.

Types of participants

We will include any person in malaria-endemic areas older than six months of age at the start of the study. For locations with endemic *P vivax* malaria, radical cure at the start of the study using a full course of 8-aminoquinolines to remove the dormant hypnozoite parasite lifecycle stage responsive for relapse, is required for inclusion.

Types of interventions

Intervention

VPSRs in any format (for example, coils, vaporizers, and passive emanator) used to prevent malaria. For studies that combine the use of these interventions with other vector control tools, such as IRS, ITNs (standard of care), or personal protection measures (for example, topical repellents or insecticide-treated clothing), we will only include and assess these if treatment allocation compares use of these interventions with and without VPSR, and sample size is sufficient to estimate the additional protective efficacy of VPSR over the other vector control interventions.

Control

Placebo or no intervention.

Types of outcome measures

Primary outcomes

- Incidence of *P falciparum* or *P vivax* malaria, measured by microscopy, mRDT, or PCR
- Prevalence *of P falciparum* or *P vivax* malaria, (measured by microscopy, mRDT, or PCR

Secondary outcomes

- Malaria-related outcomes:
  - all-cause fever;
  - anaemia (haemoglobin concentration < 10 g/dL); and
  - malaria incidence and prevalence amongst neighbouring households.
- End-user related outcomes: intervention adherence, assessed by periodic spot checking on usage of VPSRs
- Recorded adverse events: skin irritation, irritation of upper airways, nausea, headaches, and others

Search methods for identification of studies

We will use electronic searches and other methods described below to identify all relevant studies available for inclusion, regardless of language or publication status (published, unpublished, in press, and in progress). For studies where information is not available in English, we can use translators for Chinese, English, French, German, Italian, Kiswahili, Portuguese, and Spanish, and can seek additional translators if necessary.

Electronic searches

To identify published studies, we will conduct a literature search that builds upon the comprehensive search from the previous Cochrane Review, identifying RCTs on spatial repellents published after 26 June 2017 (Maia 2018). Databases to be searched from 27 June 2017 will comprise of: MEDLINE (PubMed), Embase (OVID), Cochrane Central Register of Controlled Trials, included in the Cochrane Library, CAB Abstracts (Web of Science starting 27 June 2017), LILACS (BIREME), and the Cochrane Infectious Diseases Group Specialized Register.

Searching other resources

Conference proceedings

We will search the following conference proceedings to identify relevant abstracts published from June 2017 onward:

- Multilateral Initiative on Malaria conference abstract booklets;
- The annual American Society of Tropical Medicine and Hygiene conference;
- Asia Pacific Malaria Elimination Network; and
- RBM Partnership to End Malaria.

Clinical trials registries

We will search ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform to identify potential additional trials on spatial repellents, including those that are planned or ongoing. Keywords for this search will include “spatial repellent”, “metofluthrin”, “transfluthrin”, “mosquito”, “volatile pyrethroid”, “emanator”, and “mosquito coil". Building upon findings from the

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previous Cochrane Review (Maia 2018), we will search for results submitted from 2017 onwards.

Personal communications

We will contact organizations and companies that are developing passive spatial repellents including SC Johnson, Sumitomo, Thermacell, Buedokian, the United States Department of Agriculture Center for Medical, Agricultural and Veterinary Entomology, and the Widder Brothers, as well as funders such as the Presidents Malaria Initiative (PMI), Unitaid, the Deployed Warfighter Protection Program, and the Innovative Vector Control Consortium (IVCC), for ongoing and unpublished trials, We will contact experts interviewed in a review on spatial repellents (IVCC 2020), to identify additional potential studies for inclusion.

Reference lists

We will also check the reference lists of all included studies to identify additional relevant studies.

Data collection and analysis

Selection of studies

Two review authors (IC and DM) will independently assess titles and abstracts of records identified by the searches, removing obviously irrelevant reports. Duplicate results will be identified through reference management software. For potentially relevant reports, the same review authors (IC and DM) will retrieve full text and assess these for inclusion, using an eligibility form based on the review's inclusion criteria. We will collate multiple reports of the same study so that each study, rather than each report, is the unit of interest in the review. The review authors will compare their lists of included studies for concordance with eligibility criteria, and will correspond with investigators, where appropriate, to inform eligibility. Disagreements on the eligibility of studies between the two review authors will be resolved by discussion and consensus, with arbitration by a third review author (JB) as necessary. We will list excluded studies, together with the reasons for exclusion, in a 'Characteristics of excluded studies' table. If studies are incomplete, we will include them in an ongoing studies table.

Data extraction and management

Two review authors (IC and DM) will independently extract information from the reports using pre-piloted, electronic data extraction forms (see Appendix 1). In case of differences in extracted data, the two review authors will discuss these to reach consensus, and if unresolved, further discussion will involve a third review author (JB). In case of missing data, we will contact the original study authors for clarification.

Data extracted will include the following.

- **Study design and methods:** study aims, unit of randomization (for RCTs), adjustment for clustering (for cluster-RCTs), sample size, study start and end dates, duration of participation, method of recruitment of participants, method of blinding participants and personnel, informed consent obtained, and ethical approval for study obtained.
- **Participants and setting:** country, study location, malaria endemicity, *Plasmodium* species, population description, age, inclusion criteria, exclusion criteria, baseline imbalances, withdrawals and exclusions (if not provided by outcome), subgroups measured, and subgroups reported.
- **Intervention groups**: description of intervention, description of controls, co-interventions, duration of treatment period, distances between treatment and placebo individuals or clusters, and compliance.
- **Outcomes**: description of outcome measure, number of participants, unit of analysis, and incomplete outcomes or missing data.

Individually randomized trials

For dichotomous outcomes, we will extract the number of participants experiencing each outcome and the number of participants in each treatment group. For continuous numerical outcomes, we will extract the mean and a measure of variance (that is, standard deviation (SD) or standard error (SE)). If timepoints are involved (for example, incidence), we will extract and the total person time at risk in each group or the rate ratio, and a measure of variance.

Cluster-randomized trials

For dichotomous outcomes, we will extract the number of participants/clusters randomized, number of participants/clusters by treatment arm, and measures of effect (for example, rate ratio (RR), odds ratio (OR) with confidence interval (CI) or a measure of variance). We will also extract the intraclass correlation coefficient (ICC) or coefficient of variation, and methods of adjustment for cluster-adjusted data. If timepoints are involved, we will extract the number of events aggregated by treatment arm or cluster (present or absent) in person-weeks with CI or a measure of variance.

Assessment of risk of bias in included studies

Two review authors (IC and DM) will independently use the Cochrane risk of bias (RoB) 2 tool (Sterne 2019), to assess risk of bias for each included study based on a fixed set of domains of bias for which we will ask a series of signalling questions to determine 'low' or 'high' risk of bias, or 'some concerns'. A test version of the tool is also available for cluster-RCTs (Eldridge 2021), and will be used. We will resolve any discrepancies between these assessments of bias through discussion and consultation with a third review author (JKS). Risk of bias will be summarized using graphs.

We will assess the following domains of bias for each included RCT randomized by individual and by cluster.

Bias arising from the randomization process

Sequence generation: we will describe the methods used to generate the allocation sequence in sufficient detail to allow an assessment of whether it produced comparable groups. We will regard a study as having a low risk of selection bias if the sequence generation was truly random (for example, computer-generated table of random numbers, tossing a coin), a high risk of bias if sequence generation was non-random (for example, alternate randomization, randomization by birth date), and some concerns if the randomization process was not clearly described.

Allocation concealment: we will describe the method used to conceal allocation to treatment groups before assignment. We will regard studies as having a low risk of selection bias if allocation was truly concealed (for example, central allocation of participants, use of sequentially numbered, opaque, sealed envelopes, lottery

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system), a high risk of bias if the allocation process was not concealed (for example, open randomization, unsealed or non-opaque envelopes), and some concerns if the process of concealing allocation was not described sufficiently to make a judgement.

Balance imbalance: we will assess if both arms of the trial are equally balanced at baseline using criteria including age, gender, malaria indicators, use of other interventions, socioeconomic status, housing, knowledge about malaria transmission, and occupation. Baseline differences between intervention groups will suggest the presence of bias in the randomization process.

Bias due to deviations from intended interventions

Intention-to-treat (ITT) versus per-protocol effects: we will describe whether ITT or per-protocol analysis was used. Intention-to-treat analysis quantifies the effect of assignment to interventions at baseline, assuming that participants received interventions to which they were randomized regardless of the interventions they actually received. Per-protocol analysis quantifies the effect of interventions actually received, regardless of the interventions they were assigned to. We will consider studies to have: a low risk of bias if ITT analysis was conducted with information on deviations provided that do not affect study outcomes; a high risk of bias if no information on assignment is provided; and some concerns if there is no information on deviations from the assignment of interventions assigned at baseline.

We will regard studies without ITT data (for example, studies with only per-protocol data available, where participants were analyzed according to the interventions they actually received) as having a low risk of bias if insufficient information on randomization is available and baseline imbalances do not suggest a problem with the randomization process, or 'some concerns' of bias if baseline imbalances suggest a problem with the randomization process.

Blinding of participants and personnel: we will describe whether blinding was present, who was blinded, and the methods used to blind study participants and personnel. We will regard studies as having a low risk of selection bias if blinding was present, or if the absence of blinding was unlikely to affect the outcomes, high risk of bias if blinding was absent and likely to affect results, and some concerns if blinding was not clearly described.

Bias due to missing outcome data

Incomplete outcome data: we will describe the percentage and proportion lost to follow-up, and whether attrition was balanced across groups or related to outcomes. We will regard studies as having a low risk of attrition bias if missing data were balanced across groups or clusters, high risk of bias if there were missing data or if missing data were more prevalent in one of the groups (see section on 'dealing with missing data'), and some concerns if it is unclear whether outcome data are missing.

Bias in measurement of the outcome

Incorrect analysis: we will describe whether analysis was appropriate, an analysis plan was followed, and results were adjusted for clustering.

Other bias: we will describe any important feature of included trials that could have affected the result, including whether the study design was appropriate.

Blinding of outcome assessors: we will describe whether blinding of outcome assessors was present, as well as how they were blinded. We will regard a study as having a low risk of detection bias if they were blind to knowledge about which intervention the participants received, high risk of bias if blinding was absent, and some concerns if blinding was not clearly described.

Bias in selection of the reported result

Selective outcome reporting: we will describe any discrepancies between the pre-specified outcomes in the methods section or published trial protocol and the outcomes reported and will attempt to identify outcomes that were measured but not reported on. We will regard a study as having low risk of reporting bias if it is evident that all pre-specified outcomes have been reported on, high risk of bias if it is evident that not all pre-specified outcomes were reported on, and some concerns if it is unclear whether all outcomes have been reported on.

Cluster-RCTs

In addition to the above, we will assess the following for each included RCT randomized by cluster.

Recruitment bias

We will describe whether participants were recruited before or after randomization of clusters. We will regard studies as having low risk of recruitment bias if participants were recruited before randomization of clusters, high risk of bias if they were recruited after randomization, and some concerns if information about the timing of recruitment is unclear.

Loss of clusters

We will describe number of clusters lost as well as reasons for attrition.

Compatibility with RCTs randomized by individuals

We will describe whether the intervention effects may be systematically different from individually RCTs (that is, whether it was likely that the effect size was over- or underestimated).

Measures of treatment effect

We will compare malaria incidence or prevalence between intervention and control using RRs or ORs. All results will be presented with their associated 95% CIs.

Unit of analysis issues

We will conduct separate analyses of individual and cluster-randomized datasets, indicating whether cluster-RCTs have made adjustments for clustering. If there was no adjustment for clustering, we will attempt to obtain and analyze raw data before combining them with data from individual RCTs. We will extract ICCs, coefficients of variation, and average cluster size, and calculate effective sample sizes. If ICCs are not available, we will estimate this based on other studies and investigate how results of our analysis will vary in sensitivity analysis. If the raw data cannot be obtained, we will exclude the study from analysis.

Dealing with missing data

In case of missing data, we will contact original investigators to request these data. If data are still missing, we will apply available-

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case analysis and only include available data. 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 carry out analyses on an ITT 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 assess statistical heterogeneity in each meta-analysis using the I^2 and Chi^2 statistics. We will regard heterogeneity as moderate if I^2 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 consider a Chi^2 test statistic with a P value of 0.10 or less to be indicative of statistically significant heterogeneity. We will explore clinical and methodological heterogeneity through consideration of the study populations, methods, and interventions, and by examining the study results.

Assessment of reporting biases

If there are 10 or more studies 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 visual assessment, we will explore reasons for asymmetry.

Data synthesis

For our overall analysis, we will present trials in the following order: *P falciparum* infection, *P vivax* infection, and mixed *Plasmodium* infection (more than one species of *Plasmodium* infection detected). Within each group, we will stratify whether ITNs, IRS, and/or other vector control interventions were included as standard of care, in both intervention and control groups.

We will analyse data using Review Manager 2020 software. We will use fixed-effects meta-analysis to combine data statistically 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 a fixed-effects or random-effects model based on the consideration of clinical and methodological heterogeneity between studies, as described previously.

Subgroup analysis and investigation of heterogeneity

We will explore reasons for substantial heterogeneity using subgroup analysis. Potential reasons for substantial heterogeneity include species of malaria infection, type of spatial repellent investigated, and use of VPSRs in combination with other vector control methods, including ITNs, IRS, and other repellents.

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

Sensitivity analysis

We will perform sensitivity analysis on the primary outcome to examine the effects of excluding studies with high risk of bias, excluding individual RCTs, excluding controlled trials without the use of placebos, or excluding studies with missing data on overall results. If ICC is estimated, we will carry out sensitivity analyses to investigate the impact of varying the ICC on overall results.

Summary of findings and assessment of the certainty of the evidence

We will create three summary of findings tables: one for *P falciparum* malaria, one for *P vivax* malaria, and one for mixed *Plasmodium* infections and include the following outcomes:

- effect of VPSRs versus control for preventing malaria;
- all cause fever when using VPSRs versus control;
- anaemia when using VPSRs versus control;
- malaria incidence and prevalence amongst neighbouring households when using VPSRs versus control;
- adherence to the use of VPSRs; and
- recorded adverse events when using spatial repellents versus control.

In our summary of findings tables, we will rate the certainty of evidence using the five GRADE considerations: risk of bias, consistency of effect, imprecision, indirectness, and publication bias (Schünemann 2022). The four levels of evidence certainty are, in accordance with Balshem 2011, as follows:

- high: we are very confident that the true effect lies close to that of the estimate of the effect;
- moderate: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect;
- low: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect; and
- 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-certainty evidence but can be downgraded if there are valid reasons within the five GRADE domains: risk of bias, inconsistency, indirectness, imprecision, 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). Each important outcome will be rated as one of four levels of certainty of evidence. These findings can be used to inform the WHO evaluation pathway (WHO 2020), informing noted evidence gaps for spatial repellents described in the *WHO Guidelines for Malaria* (WHO 2022).

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Editorial and peer-reviewer contributions

The following people conducted the editorial process for this article:

- Contact Editor: Dr Hellen Gelband, CIDG
- Sign-off Editor (final editorial decision): Professor Paul Garner, CIDG
- Managing Editor (selected peer reviewers, collated peer-reviewer comments, provided editorial guidance to authors, edited the article): Dr Deirdre Walshe, CIDG
- Copy Editor (copy editing): Lindsay Robertson (Cochrane Central Production Services)
- Peer-reviewers (provided comments and recommended an editorial decision): Dr Tanya Russell, James Cook University (content review), Thomas R Burkot, Australian Institute of Tropical Health and Medicine, James Cook University (content review); Dr Marty Chaplin, CIDG Statistical Editor (methods review)*; Dr Vittoria Lutje, CIDG Information Specialist (search review)*. One additional peer reviewer provided content peer review, but chose not to be publicly acknowledged.

*CIDG staff member, and provided peer-review comments on this article, but was not otherwise involved in the editorial process or decision-making for this article.

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APPENDICES

Appendix 1. Data extraction form

This is a draft data collection form. This form will be piloted by co-authors IC and DM, after which some sections can be expanded and added, and irrelevant sections can be removed. A new version of this form should be used for each study selected for inclusion in this review.

Notes on using data extraction form:

- Be consistent in the order and style you use to describe the information for each report.
- Record any missing information as unclear or not described, to make it clear that the information was not found in the study report(s), not that you forgot to extract it.
- Include any instructions and decision rules on the data collection form, or in an accompanying document. It is important to practice using the form and give training to any other authors using the form.

Review title or ID
Study ID *(surname of first author and year first full report of study was published e.g. Smith 2001)*

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(Continued)

Report ID
Report ID of other reports of this study including errata or retractions
Notes

General information

Date form completed *(dd/mm/yyyy)*
Name/ID of person extracting data
Reference citation
Study author contact details
Publication type *(e.g. full report, abstract, letter)*
Study funding sources (including role of funders)
Possible conflicts of interest (for study authors)
Notes:

Study eligibility

Study Characteristics	**Eligibility criteria** ***(Insert inclusion criteria for each characteristic as defined in the Protocol)***	**Eligibility criteria met?** **Yes**	**No**	**Unclear**	**Location in text or source *(pg & ¶/fig/table/other)***
Type of study	Randomized controlled trial				
	Cluster-randomized controlled trial				
Participants	Any person in malaria-endemic areas older than six months of age at the start of the study				
	For locations with endemic *P vivax* malaria, radical cure conducted at the start of the study				
Types of intervention	Coils, vaporizers and passive emanator volatile pyrethroid spatial repellents (VPSR)				
Types of comparison	Placebo or no intervention				
	Other vector control interventions (will only be included if treatment allocation compares the use of these interventions with and without VPSR and sample size is sufficient				

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(Continued)

	to estimate the additional protective efficacy of VPSR over the other vector control interventions)	
Types of outcome measures	Primary outcome: Prevalence or incidence of *P falciparum* or *P vivax* malaria confirmed through microscopy, malaria rapid diagnostic test, or PCR	
	All-cause fever	
	Anaemia (Hb < 10 g/dL)	
	Malaria incidence and prevalence among neighbouring households	
	Intervention adherence to regular use of VPSRs through periodic spot checking	
	Adverse events: skin irritation, irritation of upper airways, nausea, headaches	
INCLUDE	EXCLUDE	
Reason for exclusion		
Notes:		

DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW

Characteristics of included studies

1. Study design and methods

	Descriptions as stated in report/paper	**Location in text or source *(pg & ¶/fig/ table/other)***
Aim of study		
Unit of randomization *(by individuals, cluster)*		
Adjustment for clustering *(for cluster-RCTs only)*		
Total no. randomized *(or total pop. at start of study for non-RCTs)*		
Clusters *(if applicable, no., type, no. people per cluster)*		
Start date		

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(Continued)

End date	
Duration of participation ***(from recruitment to last follow-up)***	
Method of recruitment of participants ***(e.g. phone, mail, clinic patients)***	
Method of blinding participants and personnel	
Informed consent obtained	**Yes No Unclear**
Ethical approval needed/ obtained for study	**Yes No Unclear**
Notes:	

1. Population and setting

	Description *Include comparative information for each intervention or comparison group if available*	**Location in text or source***(pg & ¶/fig/table/other)*
Country		
Study location		
Malaria endemicity		
Plasmodium **species**		
Population description		
Age		
Inclusion criteria		
Exclusion criteria		
Baseline imbalances		
Withdrawals and exclusions *(if not provided below by outcome)*		
Subgroups measured		
Subgroups reported		
Primary vector		
Notes:		

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1. Intervention groups

Copy and paste table for each intervention and comparison group

Intervention Group 1

	Description as stated in report/paper	**Location in text or source***(pg & ¶/fig/table/other)*
Group name		
No. randomized to group*(specify whether no. people or clusters)*		
Theoretical basis*(include key references)*		
Description*(include sufficient detail for replication, e.g. content, dose, components)*		
Duration of treatment period		
Co-interventions		
Compliance		
Notes:		

Control group 1

	Description as stated in report/paper	**Location in text or source***(pg & ¶/fig/table/other)*
Group name		
No. randomized to group*(specify whether no. people or clusters)*		
Theoretical basis*(include key references)*		
Description*(include sufficient detail for replication, e.g. content, dose, components)*		
Duration of treatment period		
Co-interventions		
Compliance		
Notes:		

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1. Outcomes

Copy and paste table for each outcome.

Outcome 1

	Description as stated in report/paper	**Location in text or source***(pg & ¶/fig/ table/other)*
Outcome name	Malaria incidence (primary outcome)	
Time points measured *(specify whether from start or end of intervention)*		
Time points reported		
Outcome definition*(malaria diagnosis by mRDT, thick or thin blood smear, PCR)*		
Person measuring/reporting		
Unit of measurement*(if relevant)*		
Is outcome/tool validated?	Yes No Unclear	
Imputation of missing data *(e.g. assumptions made for ITT analysis)*		
Assumed risk estimate *(e.g. baseline or population risk of malaria noted in Background)*		
Power*(e.g. power & sample size calculation, level of power achieved)*		
Notes:		

Outcome 2

	Description as stated in report/paper	**Location in text or source***(pg & ¶/fig/ table/other)*
Outcome name	Malaria prevalence (primary outcome)	

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Time points measured *(specify whether from start or end of intervention)*	
Time points reported	
Outcome definition*(malaria diagnosis by mRDT, thick or thin blood smear, PCR)*	
Person measuring/reporting	
Unit of measurement*(if relevant)*	
Is outcome/tool validated?	Yes No Unclear
Imputation of missing data *(e.g. assumptions made for ITT analysis)*	
Assumed risk estimate *(e.g. baseline or population risk of malaria noted in Background)*	
Power*(e.g. power & sample size calculation, level of power achieved)*	
Notes:	

Outcome 3

	Description as stated in report/paper	**Location in text or source***(pg & ¶/fig/table/other)*
Outcome name	All cause fever	
Time points measured *(specify whether from start or end of intervention)*		
Time points reported		
Outcome definition*(malaria diagnosis by mRDT, thick or thin blood smear, PCR)*		
Person measuring/reporting		
Unit of measurement*(if relevant)*		
Is outcome/tool validated?	Yes No Unclear	
Imputation of missing data *(e.g. assumptions made for ITT analysis)*		

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(Continued)

Assumed risk estimate *(e.g. baseline or population risk of fever noted in Background)*	
Notes:	

Outcome 4

	Description as stated in report/paper	**Location in text or source***(pg & ¶/fig/table/other)*
Outcome name	Anemia (Hb concentration < 10 g/dL)	
Time points measured *(specify whether from start or end of intervention)*		
Time points reported		
Outcome definition*(malaria diagnosis by mRDT, thick or thin blood smear, PCR)*		
Person measuring/reporting		
Unit of measurement*(if relevant)*		
Is outcome/tool validated?	Yes No Unclear	
Imputation of missing data *(e.g. assumptions made for ITT analysis)*		
Assumed risk estimate *(e.g. baseline or population risk of anemia noted in Background)*		
Notes:		

Outcome 5

	Description as stated in report/paper	**Location in text or source***(pg & ¶/fig/table/other)*
Outcome name	Malaria incidence and prevalence among neighboring households	

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(Continued)

Time points measured *(specify whether from start or end of intervention)*	
Time points reported	
Outcome definition*(malaria diagnosis by mRDT, thick or thin blood smear, PCR)*	
Person measuring/reporting	
Unit of measurement*(if relevant)*	
Is outcome/tool validated?	Yes No Unclear
Imputation of missing data *(e.g. assumptions made for ITT analysis)*	
Notes:	

Outcome 6

	Description as stated in report/paper	**Location in text or source***(pg & ¶/fig/table/other)*
Outcome name	Intervention adherence to regular usage of volatile pyrethroid spatial repellents through periodic spot checking	
Time points measured *(specify whether from start or end of intervention)*		
Time points reported		
Outcome definition*(malaria diagnosis by mRDT, thick or thin blood smear, PCR)*		
Person measuring/reporting		
Unit of measurement*(if relevant)*		
Is outcome/tool validated?	Yes No Unclear	
Imputation of missing data *(e.g. assumptions made for ITT analysis)*		
Notes:		

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Outcome 7

	Description as stated in report/paper	**Location in text or source***(pg & ¶/fig/ table/other)*
Outcome name	Recorded adverse events, such as skin irritation, irritation of upper airways, nausea, headaches, and others.	
Time points measured *(specify whether from start or end of intervention)*		
Time points reported		
Outcome definition*(malaria diagnosis by mRDT, thick or thin blood smear, PCR)*		
Person measuring/reporting		
Unit of measurement*(if relevant)*		
Is outcome/tool validated?	Yes No Unclear	
Imputation of missing data *(e.g. assumptions made for ITT analysis)*		
Notes:		

1. Data and analysis

Copy and paste the appropriate table for each outcome, including additional tables for each time point and subgroup as required.

Outcome 1. Continuous outcome

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		Description as stated in report/paper				Location in text or source *(pg & ¶/fig/table/other)*
Comparison						
Outcome		Incidence of *P falciparum* or *P vivax* malaria measured by microscopy, mRDT, or PCR (primary outcome)				
Subgroup						
Time point *(specify from start or end of intervention)*						
Post-intervention or change from baseline?						
Results	Intervention			Comparison		
	Mean	SD *(or other variance, specify)*	No. participants	Mean	SD *(or other variance, specify)*	No. participants
Any other results reported *(e.g. mean difference, CI, P value)*						
No. missing participants						
Reasons missing						
No. participants moved from other group						
Reasons moved						
Unit of analysis *(individuals, cluster/ groups or body parts)*						
Statistical methods used and appropriateness of these *(e.g. adjustment for correlation)*						
Reanalysis required? *(specify)*		Yes No Unclear				
Reanalysis possible?		Yes No Unclear				
Reanalysed results						

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(Continued)

Notes:

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Outcome 2. Dichotomous outcome

	Description as stated in report/paper				Location in text or source *(pg & ¶/fig/table/other)*
Comparison					
Outcome	Prevalence of *P falciparum* or *P vivax* malaria measured by microscopy, mRDT, or PCR (primary outcome)				
Subgroup					
Time point *(specify from start or end of intervention)*					
Results	Intervention		Comparison		
	No. with event	Total in group	No. with event	Total in group	
Any other results reported *(e.g. odds ratio, risk difference, CI or P value)*					
No. missing participants					
Reasons missing					
No. participants moved from other group					
Reasons moved					
Unit of analysis *(by individuals, cluster/groups)*					
Statistical methods used and appropriateness of these *(e.g. adjustment for correlation)*					
Reanalysis required? *(specify, e.g. correlation adjustment)*	Yes No Unclear				
Reanalysis possible?	Yes No Unclear				
Reanalysed results					
Notes:					

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Outcome 3. Dichotomous outcome

	Description as stated in report/paper				Location in text or source *(pg & ¶/fig/table/other)*
Comparison					
Outcome	All-cause fever				
Subgroup					
Time point *(specify from start or end of intervention)*					
Results	Intervention		Comparison		
	No. with event	Total in group	No. with event	Total in group	
Any other results reported *(e.g. odds ratio, risk difference, CI or P value)*					
No. missing participants					
Reasons missing					
No. participants moved from other group					
Reasons moved					
Unit of analysis *(by individuals, cluster/groups)*					
Statistical methods used and appropriateness of these *(e.g. adjustment for correlation)*					
Reanalysis required? *(specify, e.g. correlation adjustment)*	Yes No Unclear				
Reanalysis possible?	Yes No Unclear				
Reanalysed results					
Notes:					

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Outcome 4. Continuous outcome

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		Description as stated in report/paper				Location in text or source *(pg & ¶/fig/table/other)*
Comparison						
Outcome		Anemia (Hb concentration < 10 g/dL)				
Subgroup						
Time point *(specify from start or end of intervention)*						
Post-intervention or change from baseline?						
Results	Intervention			Comparison		
	Mean	SD *(or other variance, specify)*	No. participants	Mean	SD *(or other variance, specify)*	No. participants
Any other results reported *(e.g. mean difference, CI, P value)*						
No. missing participants						
Reasons missing						
No. participants moved from other group						
Reasons moved						
Unit of analysis *(individuals, cluster/ groups or body parts)*						
Statistical methods used and appropriateness of these *(e.g. adjustment for correlation)*						
Reanalysis required? *(specify)*		Yes No Unclear				
Reanalysis possible?		Yes No Unclear				
Reanalysed results						

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(Continued)

Notes:

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Outcome 5. Continuous or dichotomous outcome

	Description as stated in report/paper				Location in text or source *(pg & ¶/fig/table/other)*
Comparison					
Outcome	Malaria incidence and prevalence among neighboring households				
Subgroup					
Time point *(specify from start or end of intervention)*					
Results	Intervention		Comparison		
	No. with event	Total in group	No. with event	Total in group	
Any other results reported *(e.g. odds ratio, risk difference, CI or P value)*					
No. missing participants					
Reasons missing					
No. participants moved from other group					
Reasons moved					
Unit of analysis *(by individuals, cluster/groups)*					
Statistical methods used and appropriateness of these *(e.g. adjustment for correlation)*					
Reanalysis required? *(specify, e.g. correlation adjustment)*	Yes No Unclear				
Reanalysis possible?	Yes No Unclear				
Reanalysed results					
Notes:					

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Outcome 6. Dichotomous outcome

	Description as stated in report/paper				Location in text or source *(pg & ¶/fig/table/other)*
Comparison					
Outcome	Intervention adherence to regular usage of VPSRs through periodic spot checking.				
Subgroup					
Time point *(specify from start or end of intervention)*					
Results	Intervention		Comparison		
	No. with event	Total in group	No. with event	Total in group	
Any other results reported *(e.g. odds ratio, risk difference, CI or P value)*					
No. missing participants					
Reasons missing					
No. participants moved from other group					
Reasons moved					
Unit of analysis *(by individuals, cluster/groups)*					
Statistical methods used and appropriateness of these *(e.g. adjustment for correlation)*					
Reanalysis required? *(specify, e.g. correlation adjustment)*	Yes No Unclear				
Reanalysis possible?	Yes No Unclear				
Reanalysed results					
Notes:					

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Outcome 7 (Descriptive outcome)

	Description as stated in report/paper				Location in text or source *(pg & ¶/fig/table/other)*
Comparison					
Outcome	Recorded adverse events, such as skin irritation, irritation of upper airways, nausea, headaches, and others.				
Subgroup					
Time point *(specify from start or end of intervention)*					
No. participant	Intervention		Control		
Results	Intervention result	SE (or other variance)	Control result	SE (or other variance)	
	Overall results		SE (or other variance)		
Any other results reported					
No. missing participants					
Reasons missing					
No. participants moved from other group					
Reasons moved					
Unit of analysis *(by individuals, cluster/groups or body parts)*					
Statistical methods used and appropriateness of these					
Reanalysis required? *(specify)*	Yes No Unclear				
Reanalysis possible?	Yes No Unclear				
Reanalysed results					
Notes:					

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Other information

	Description as stated in report/paper	Location in text or source *(pg & ¶/fig/table/other)*
Key conclusions of study authors		
References to other relevant studies		
Correspondence required for further study information*(from whom, what and when)*		
Notes:		

Appendix 2. Draft MEDLINE search strategy

This strategy will be adapted to search other electronic databases listed in the Methods section, searching results published on or after 1 January 2017.

Search set	Search terms
1	"Mosquito Control" [Mesh]
2	"Anopheles" [Mesh]
3	Malaria* ti, ab
4	Spatial repellent* ti, ab
5	Transfluthrin OR metofluthrin OR volatile pyrethroid OR passive emanator OR ambient emanator OR mosquito coil ti, ab
6	Randomized controlled trial ti, ab
7	Incidence OR prevalence ti, ab
8	(1 and 4) or (2 and 4) or (3 and 4)
9	(4 or 5) and (6 or 7)
10	8 and 9

CONTRIBUTIONS OF AUTHORS

IC wrote the first draft of the protocol. SM, NL, and JB edited the protocol, and all authors approved the protocol prior to publication.

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DECLARATIONS OF INTEREST

ITC holds an NIH grant, and has no known conflicts of interest.
JKS has no known conflicts of interest.
DM has no known conflicts of interest.
NFL was involved in three studies potentially eligible for inclusion in this review. Each non-company funded grant was utilized to evaluate a product for the reduction of exposure to entomological or epidemiological endpoints (primarily malaria); products were donated by SCJohnson and Widder Bros. He has no known conflicts of interest.
JB has no known conflicts of interest.
SJM has no known conflicts of interest.

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