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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
BACKGROUND	1
OBJECTIVES	3
METHODS	3
ACKNOWLEDGEMENTS	7
REFERENCES	8
APPENDICES	9
CONTRIBUTIONS OF AUTHORS	10
DECLARATIONS OF INTEREST	10
SOURCES OF SUPPORT	10

[Intervention Protocol]

Mosquito repellents for malaria prevention

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To summarise the effects of repellents on preventing new cases of *Plasmodium falciparum* and *Plasmodium vivax* malaria.

Specifically, to summarise and evaluate the effect of:

1. Insecticide treated clothing (ITC);
2. Topical repellents; and
3. Spatial repellents.

BACKGROUND

Description of the condition

Malaria is caused by protozoan parasites of the genus *Plasmodium*. The most severe form of the disease is caused by *P. falciparum*. Other *Plasmodium* species known to cause milder cases of malaria include *P. vivax*, *P. ovale* and *P. malariae*. The parasites are transmitted to people through the bite of an infected *Anopheles* mosquito. Malaria is wide spread in tropical and subtropical regions and is considered endemic in 104 countries worldwide (WHO 2013). Symptoms of malaria include fever, chills, headache, and vomiting, and usually appear between 10 to 15 days after the bite of an

infected mosquito. If left untreated, the person may develop severe complications and malaria can quickly become life-threatening by disrupting the blood supply to vital organs. Diagnosis is done through identification of the *Plasmodium* parasite in the patient's bloodstream, usually by microscopic examination of a blood slide or malaria rapid diagnostic tests (mRDTs).

In the past decade, great advances have been made in the fight against malaria. From 2000 to 2012 global incidence of malaria reduced by 30% and related mortality by 50% (WHO 2013). This is due to massive scale-up of the vector control interventions using long lasting insecticide-treated bed nets (LLINs) and indoor residual spraying (IRS), as well as introduction of mRDTs for better malaria diagnosis and use of highly effective artemisinin-based

combination therapies (ACTs). Despite these developments, an estimated 3.3 billion people living in 104 countries are still at risk of contracting malaria and, as a result, 1300 children under 5 years old die every day in malaria endemic regions (WHO 2013). While the vector control component of most national malaria control programmes concentrates on distribution of LLINs and IRS, there is substantial malaria transmission within and outside Africa at times when people are outdoors (Durnez 2013). Recent estimates are that 16% of global malaria burden and 8% of malaria mortality occurs outside Africa (WHO 2013) where vectors are primarily early evening feeders (Sinka 2010; Sinka 2011). In order to achieve sustained malaria control and move towards malaria elimination, new tools will be required to interrupt transmission in environments where existing tools are not completely effective (malERA 2011). Residual malaria transmission is maintained by the presence of asymptomatic carriers, the significant number of non compliant LLIN users, early evening outdoor feeding *Anopheles* mosquitoes and the spread of drug and insecticide resistance (White 2014). As well as preventing early evening bites, mosquito repellents may be suitable for people who have a high occupational risk of contracting malaria, such as: those working at night particularly in mining; soldiers; people in close contact with forest ecosystems; and migrants (Onyango 2014). It is well known that these high-risk individuals “re-seed” malaria in areas where vector control activities are carried out (Tatem 2010). With the impetus for malaria eradication of the past decade and the realization that the existing control tools cannot solely achieve this, mosquito repellents are increasingly being considered as supplementary tools in some malaria endemic settings (Sturrock 2013).

Description of the intervention

Personal protection has been used for centuries to prevent mosquito bites (Herodotus 1996). Historically, people burned repellent plants and applied essential oils directly onto their skin or clothing. In recent times industry has developed more effective products that have largely replaced traditional methods, including mosquito coils, long-lasting formulated repellent lotions and insecticide treatments for clothing. Mosquito repellents are currently recommended by the World Health Organization (WHO) as the first-line malaria prevention tool for travellers (WHO 2012) and are commonly used by expatriates in tropical developing countries. There are three main interventions that result in mosquito bite prevention:

1. Wearing insecticide-treated clothing (ITC);
2. Applying topical repellents directly onto the skin; and
3. Using spatial repellents.

The mode of action of these three intervention types on the mosquito is not the same, however they all result in preventing mosquito bites and so potentially reduce transmission of *Plasmodium* parasites from infected mosquitoes to humans.

ITC

ITC is widely used by military personnel to protect against vector borne diseases and biting nuisance (Kitchen 2009). The synthetic pyrethroid permethrin (2 g/m²) is used most commonly for treatment of clothing. Permethrin is approved by the WHO for this purpose because of its low dermal absorption, low mammalian toxicity, no odour and minimal irritation (WHOPES 2006). The mode of action of ITC is through contact irritancy, whereby mosquitoes make oriented movement away from the person after physical contact with the treated clothing surface, and it also affects mosquito feeding response. Both of these modes of actions result in a reduction in mosquito bites to the ITC user.

Topical repellents

Topical repellents may contain a wide range of active ingredients and are available in various formulations, lotions, gels, roll-ons, and on wipes. Approved active ingredients for mosquito-borne disease prevention are DEET (chemical name: N,N-diethyl-m-toluamide or N,N-diethyl-3-methyl-benzamide), icaridin (KBR 3023 [Bayrepel] and picaridin inside the United States; chemical name: 2-2-hydroxyethyl-1-piperidinecarboxylic acid 1-methylpropyl ester), PMD (para-methane-3,8-diol), and IR3535 (chemical name: 3-[N-butyl-N-acetyl]-aminopropionic acid, ethyl ester) (WHO 2012; CDC 2014). The Environmental Protection Agency (EPA) estimated that approximately 200 million people are exposed annually to DEET worldwide (WHOPES 1998). Each repellent molecule has a different mode of action on mosquito olfactory receptors, but all prevent mosquito bloodfeeding and result in reduced man-biting rates.

Spatial repellents

Spatial repellents disperse active ingredients into the surrounding air that interfere with the mosquito's ability to find a host, thus preventing mosquitoes from taking a blood meal. They may interfere with host detection or through excito-repellency, causing insects to fly in an undirected manner until they eventually move away from the source of repellent vapour. Spatial repellents create a protective area within a given radius and can be used to protect more than one person at the same time. Dispersal of the active ingredient can be done in two ways:

1. Through heat (for example, mosquito coil and electric emanators); or
2. Through evaporation (for example, passive emanators made of paper or agarose gel).

The most popular format is the mosquito coil and an estimated 45 to 50 billion mosquito coils are used annually by approximately two billion people worldwide, mainly in Southeast Asia (Zhang 2010). Mosquito coils are made from a mixture of inert ingredients, such as sawdust or coconut husks, and pigment that burns at a low temperature dispersing the active ingredient, usually a

volatile pyrethroid with a quick knock-down action (for example, pyrethrin, D-allethrin, transfluthrin, or metofluthrin). The smoke produced by the burning of mosquito coils can cause indoor air pollution.

Electric emanators consist of an electrical heating agent that vaporizes insecticide that has been impregnated into a pad or wick. These produce no smoke but require a source of electricity, which is not available in a large proportion of the homes in malaria-endemic countries.

Passive emanators do not require a source of heat or combustion. They have a large surface area which allows the passive dispersal of the volatile active ingredient into the air by evaporation without the need for an external source of energy. The chosen active ingredients are predominantly less polar compounds that are easily volatilised. Examples include metofluthrin and transfluthrin.

How the intervention might work

During the first Global Malaria Eradication Campaign the concept of vectorial capacity was developed and validated to mathematically evaluate the impact of mosquito control interventions on malaria transmission using several measurable field parameters (Garrett-Jones 1964). Vectorial capacity is defined as: “the daily rate at which future inoculations of a parasite arise from a currently infective case, provided that all female vectors biting that case become infected” (Garrett-Jones 1964). The original validation demonstrated that by reducing man-vector contact (mosquito bites) by 50% there was a consequent 75% reduction in vectorial capacity. Man-vector contact can be reduced by using repellents. Mosquitoes will be repelled or disabled from feeding on a person while being exposed to the repellent. These personal protective measures can be used at any time or location, and so are suitable for controlling mosquitoes biting outdoors and during early evening hours before people retire to bed. Repellents also protect individuals from all mosquito-borne diseases because they stop the mosquito from biting and therefore prevent transmission of pathogens through the mosquito bite.

Why it is important to do this review

The wide distribution of LLINs in malaria-endemic countries has resulted in a considerable reduction of malaria incidence and prevalence throughout affected areas (WHO 2013). However, LLINs only protect people while they are under them. It is estimated that in South America and Southeast Asia 80% of malaria transmission occurs before sleeping hours. Even in Africa, where *Anopheles* mosquitoes vectors are traditionally late feeders, up to 20% of malaria transmission is taking place during early evening and early morning hours (Onyango 2014). During this time the only available means of protection are repellents and ITC. These interventions may reduce existent residual malaria transmission,

by protecting people outside of LLINs. This Cochrane Review aims to measure the effectiveness of these interventions in reducing the incidence of malaria alone and when combined with LLINs to facilitate decision makers considering including repellents in national malaria control programmes. In addition, we believe that this review may be helpful to reach three of the United Nations Millennium Development Goals (MDGs):

- MDG 04: To reduce child mortality rates. Reducing the number of mosquito bites a child receives has been shown to lower the morbidity from malaria (Snow 1998). Repellents may also reduce other vector-borne diseases as the most widely used repellents are broad spectrum and prevent bites from a range of disease vectors.
- MDG 05: To improve maternal health. Pregnant women are more attractive to mosquitoes and therefore at a higher risk of infection than when the same women are not pregnant. In addition, pregnant women are particularly susceptible to complications of malaria. Modern repellents are safe to use among pregnant women and therefore have the potential to confer protection to a high-risk group.
- MDG 06: To combat HIV/AIDS, malaria, and other diseases.

OBJECTIVES

To summarise the effects of repellents on preventing new cases of *Plasmodium falciparum* and *Plasmodium vivax* malaria.

Specifically, to summarise and evaluate the effect of:

1. Insecticide treated clothing (ITC);
2. Topical repellents; and
3. Spatial repellents.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs), randomized by cluster or individual.

Types of participants

Adults and children living in malaria-endemic areas.

In areas endemic for *P. vivax*, we will only include trials in which participants have been screened at the trial start and *Plasmodium* parasites have been cleared. Thus, only new cases of malaria that are preventable by the intervention, and not recrudescence of a dormant infection, will be measured.

Types of interventions

We will include trials with or without LLINs in both trial arms.

Intervention

- ITC impregnated with permethrin; or
- Topical repellents including DEET, icaridin, IR3535 and PMD; or
- Spatial repellents including transfluthrin coils, metofluthrin coils, D-allethrin coils, pyrethrin coils, metofluthrin emanators and transfluthrin emanators.

Control

Individuals given a placebo or no treatment.

Types of outcome measures

Primary outcomes

- Clinical malaria confirmed through blood smears or rapid diagnostic tests (*P. falciparum* or *P. vivax*).
- Participants with *Plasmodium* parasitaemia confirmed through thick or thin blood smears, mRDTs, or polymerase chain reaction (PCR) (*P. falciparum* or *P. vivax*).

Secondary outcomes

- Anaemia (haemoglobin < 8 g/dL);
- Time to first infection (days);
- All-cause fever;
- Adherence to regular usage of the intervention measured through spot-checking per period of time; and
- Reduction in mosquitoes attempting to feed on humans.

Recorded adverse events

- Skin irritation;
- Irritation of upper airways;
- Nausea; and
- Headaches.

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; EMBASE; United States Armed Forces Pesticide Management Board (US AFPMB); CAB Abstracts; and LILACS up to present. We will also search the WHO International Clinical Trials Registry Platform and the metaRegister of Controlled Trials (mRCT) using 'mosquito*', 'malaria', DEET, PMD, IR3535, Icaridin, Metofluthrin, Transfluthrin, and repellent,* as search terms.

Searching other resources

Conference proceedings

We will search the following conference proceedings of the relevant abstracts:

- MIM conference abstract booklets (2008 to present);
- Annual ASTMH conference (2008 to present);
- Entomological Society of America (2008 to present); and
- Society of Vector Ecology of America (2008 to present).

Organisations and pharmaceutical companies

We will contact organizations including the WHO, and Centers for Disease Control and Prevention (CDC), United States Department of Agriculture (USDA), United States Agency for International Development (USAID), US AFPMB, Deployed War Fighter Protection Program (DWFPP) and chemical companies including Bayer, Sumitomo, Vestergaard-Frandsen, BASF, SC Johnson, Insect Shield, Mosiguard, Sara Lee, Syngenta, and other local companies for ongoing and unpublished trials.

Reference lists

We will also check the reference lists of all included trials for further relevant studies.

Data collection and analysis

Selection of studies

Three review authors (MM, MK, and SM) will independently assess the titles and abstracts of trials identified by the searches. The same three review authors will assess full text copies of potentially relevant trials for inclusion using an eligibility form based on inclusion criteria. We will compare included trials, and resolve any disagreements by discussion and consensus, with arbitration by the fourth review author (CL) 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 table format.

Data extraction and management

Three review authors (MM, MV, and SM) will independently extract information from the trials using pre-piloted, electronic data extraction forms. In case of differences in extracted data, the three review authors will discuss these differences to reach consensus. If unresolved, further discussion will involve the fourth author (CL). In case of missing data, we will contact the original trial author(s) for clarification. We will include all RCTs published in Chinese journals after contacting the trial authors and determining the adequacy of randomization (Wu 2009).

We will extract data on the following:

1. Trial design: Type of trial; method of participant selection; unit of randomization (for RCTs); adjustment for clustering (for cluster RCTs (cRCTs)); sample size; method of blinding of participants and personnel; diagnostic method; primary vector; vector biting time; malaria endemicity; *Plasmodium* species;
2. Participants: Trial settings and population characteristics; recruitment rates; withdrawal and loss to follow-up;
3. Intervention: Description of intervention; co-interventions; description of controls; time of follow-up; passive or active case detection; compliance; and
4. Outcomes: Definition of outcome; number of events; number of participants; power; unit of analysis; incomplete outcomes/missing data.

For dichotomous outcomes, we will extract the number of patients experiencing each outcome and the number of patients in each treatment group. For count 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 numerical outcomes, that is time to first infection (days), we will extract the mean and a measure of variance (standard deviation).

RCTs randomized by the individual

We will extract information on the number of participants randomized to each treatment arm; and the number of events in each of the treatment arms (present or absent) in person/weeks.

cRCTs

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 intra-cluster correlation coefficient (ICC) value.

Assessment of risk of bias in included studies

Three review authors (MM, MK, and SM) will independently assess risk of bias for each included trial using the the Cochrane Collaboration's 'Risk of bias' tool (Higgins 2011). Any discrepancies will be resolved through discussion or by consulting the fourth review author (CL). We will classify judgements of risk of bias as either low, high or unclear risk of bias, using summary graphs ('Risk of bias' summary and 'Risk of bias' graph) to display results. We will assess each of the following components for each included RCT randomized by the individual and by cluster:

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 trial 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 unclear risk of bias if the randomization process was not clearly described.

Balance

Regarding balance, we will assess if both arms of the trial are equally balanced at baseline using criteria including age, gender, malaria indicators, socioeconomic status, housing, use of other interventions, knowledge about malaria transmission, and occupation.

Allocation concealment

We will describe the method used to conceal allocation to treatment groups before assignment. We will regard trials 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 system); a high risk of bias if the allocation process was not concealed (for example, open randomization, unsealed or non-opaque envelopes); and an unclear risk of bias if the process of concealing allocation was not described sufficiently to make a judgement.

Blinding of participants and personnel

We will describe whether blinding was present, who was blinded, and the methods used to blind trial participants and personnel. We will regard a trial as having a low risk of performance 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 the results; and unclear risk of bias if blinding was not clearly described.

Blinding of outcome assessors

Regarding blinding of outcome assessors, we will describe whether blinding of outcome assessors was present, and how they were blinded. We will regard a trial as having a low risk of detection bias if they were blinded to knowledge about which intervention the participants received; high risk of bias if blinding was absent; and unclear risk if blinding was not clearly described.

Incomplete outcome data

We will describe the percentage and proportion loss to follow-up; reasons for attrition; and whether attrition was balanced across groups or related to outcomes. We will regard trials as having a low risk of attrition bias if there was no missing data or if missing data was balanced across groups or clusters; high risk of bias if there was missing data or if missing data was more prevalent in one of the groups; and unclear risk of bias if it is unclear whether outcome data is missing.

Selective outcome reporting

We will record any discrepancies between the pre-specified outcomes in the methods section and the outcomes reported, and will attempt to identify outcomes that were measured but not reported on. We will regard a trial 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 unclear risk of bias if it is unclear whether all outcomes were reported on.

Incorrect analysis

We will describe whether the analysis was appropriate, an analysis plan was followed, and if it was adjusted for clustering.

Other bias

We will describe any important feature of included trials that could have affected the result.

In addition to the above, we will assess the following for each included cRCT:

Recruitment bias

Regarding recruitment bias, we will describe whether participants were recruited before or after randomization of clusters. We will regard trials 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 unclear risk of bias if information about the timing of recruitment is unclear.

Loss of clusters

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

Compatibility with RCTs randomized by individuals

We will note 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 intervention and control data using risk ratios. All results will be presented with their associated 95% CIs.

Unit of analysis issues

We will combine results from cRCTs with individually RCTs if they have adjusted for clustering in their analysis and present results using forest plots. If there was no adjustment for clustering in RCTs, we will attempt to adjust data before combining it with data from individually RCTs. We will attempt to adjust the data by multiplying standard errors by the square root of the design effect (Higgins 2011). If the trial does not report the ICC value, then we will estimate the ICC from a similar trial if possible, or by searching external sources for example ICCs. Alternatively, we will not include cRCTs that have not adjusted for clustering in the meta-analysis but will present results in a separate table.

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 carry out 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 to.

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 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. Clinical and methodological heterogeneity will be explored through consideration of the trial populations, methods and interventions, and by visualisation 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 (Harbord 2006) for funnel plot asymmetry. If we detect asymmetry in any of these tests or by a visual assessment, we will explore reasons for asymmetry.

Data synthesis

We will group trials and analyse by intervention:

1. Topical repellents;
2. Spatial repellents;
3. ITC.

Within each group, we will stratify by whether LLINs were included in both intervention and control groups.

We will analyse data using Review Manager 2014 software. 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 or random-effects based on the consideration of clinical and methodological heterogeneity between trials, as described previously.

Quality of evidence

We will rate the quality of evidence using the GRADE approach (Guyatt 2011). Each important outcome will be rated as described by Balshem 2011:

1. High: We are very confident that the true effect lies close to that of the estimate of the effect;
2. Moderate: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect;
3. Low: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect; or
4. 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:

1. Malaria prevalence in children under five years old:
 - i) Holoendemic ($> 20\%$);
 - ii) Mesoendemic (10 to 20%);
 - iii) Hypoendemic ($< 10\%$).
2. Measure of compliance with intervention:
 - i) High ($> 80\%$);
 - ii) Moderate (50 to 80%);
 - iii) Low ($< 50\%$).
3. Malaria diagnostic method:
 - i) mRDTs;
 - ii) Blood smear (thick or thin);
 - iii) PCR.

We will assess differences between subgroups using the Chi^2 test, with a P value ≤ 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 overall results. The same analysis will be done to investigate whether the exclusion of cRCTs affects results, as well as whether being placebo-controlled; and to see what effect missing data has on results. If the ICC value is estimated, we will carry out sensitivity analyses to investigate the impact of varying the ICC on results from the meta-analysis.

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* Indicates the major publication for the study

APPENDICES

Appendix I. Search strategy

Search set	Search terms ^a
1	Malaria* ti, ab
2	“Insect Vectors”[Mesh] OR vector* ti, ab OR mosquito* ti, ab
3	1 or 2
4	“Mosquito Control”[Mesh]
5	“Anopheles”[Mesh]
6	3 or 4 or 5
7	Repellen* ti, ab
8	“Insecticide treated clothing” OR ITC ti,ab
9	Spray OR sprays OR lotion* OR gel OR gels OR roll-on* OR wipe* ti, ab
10	Coil* ti, ab
11	“passive emanator*” ti, ab
12	“electric emanator*” ti, ab
13	“vaporizer mat*” ti, ab
14	“personal protection*” ti, ab

(Continued)

15	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16	6 and 15

^aSearch terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration ([Lefebvre 2011](#)).

This is the preliminary search strategy we will use for MEDLINE (Pubmed). We will adapt it to search the other electronic databases listed in the [Methods](#) section. All search strategies will be reported in full in the final version of the review.

CONTRIBUTIONS OF AUTHORS

MM, MV, and SM drafted the protocol. MR provided statistical support. CL advised on the protocol.

DECLARATIONS OF INTEREST

SM is an investigator of a RCT on mosquito repellents for malaria prevention but will have no part in deciding inclusion, assessment of risk of bias, data extraction or interpretation of the results of this trial. If included, MM, MK and CL (who have no known conflicts of interests) will evaluate the trial.

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