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[Intervention Protocol]

Topical 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 effect of topical repellents alone or in combination with other background interventions for reducing malaria incidence in high-risk and non-high-risk populations living in endemic areas.

BACKGROUND

Description of the condition

Malaria is arguably the most important parasitic disease in the world. Five species of protozoan parasites from the genus *Plasmodium* regularly infect humans: *P falciparum*, *P vivax*, *P ovale*, *P malariae*, and *P knowlesi.* Over 229 million cases of malaria were estimated to have occurred in 2019, 94% of which occurred in Africa (WHO 2020a). All of these parasites are transmitted by the bite of female mosquitoes from over 40 species of the genus *Anopheles*, which are widely spread throughout tropical and subtropical regions around the world (Sinka 2012). Malaria has a wide clinical presentation, with most cases characterized by the presence of mild unspecific signs, such as fever, chills, headache, nausea, and malaise. However, cases caused by *P falciparum,* which account for 98% of all cases in Africa, can cause severe disease and death if untreated. Severe disease is usually characterized by impaired consciousness, respiratory distress, hypoglycaemia, and severe anaemia. Infection with *P knowlesi,* the most important zoonotic species, is restricted to South East Asia and is also often associated with complications. Infection with *P vivax*, *P ovale*, and *P malariae* is generally associated with fewer complications and deaths. Simian species of malaria such as *P cynomolgi* and *P inui*, among others, can occasionally infect humans, but are not considered to be of relevance to public health (Vythilingam 2021).

Significant advances in malaria control have been achieved in the last two decades, mostly by the development and wide distribution of commodity-based preventive measures. These measures include long-lasting insecticide treated nets (LLINs), artemisinin-based combination therapies (ACTs), and inexpensive, easily scalable rapid diagnostic tests (mRDTs) (WHO 2020a). This has translated into a 27.5% reduction in global malaria incidence (measured as cases per 1000 people at risk), and a 44.4% reduction in malaria deaths between 2000 and 2019 (WHO 2020a). Unfortunately, progress has slowed down in the last six years. The World Health Organization's (WHO) 2016 – 2030 Global Technical Strategy for Malaria (GTS) presented the ambitious goal of reducing global incidence by 40% by 2020, and by 90% by 2030, compared to 2015 figures (WHO 2015). The world remains off-track of meeting this target, with a global incidence reduction of less than 2% between 2015 and 2019 (WHO 2020a). Many obstacles, including poor access to health systems, political unrest, or poor commitment to malaria control, hold accountability. New interventions might bring the world closer to that goal, as long as they reach those who can benefit from them.

Insecticide-based interventions, LLINs, and indoor residual spraying (IRS), are the backbone of current malaria vector control. In settings where pyrethroid resistance is established, these interventions are thought to remain effective at reducing transmission through sublethal effects (Kleinschmidt 2018). However, their effectiveness in reducing malaria transmission is dependent on adequate coverage. Furthermore, they only target mosquito species that feed predominantly on humans and in indoor settings, mostly protecting people indoors and while they sleep. While these interventions are useful in Africa, where anthropophilic and endophilic vectors are dominant, their efficacy is considerably lower in other settings where mosquito species have different feeding and resting habits (Steinhardt 2017). Another important concern is the persistence of residual malaria transmission (Killeen 2014), whereby malaria elimination cannot be achieved despite optimal coverage of effective interventions. Selective pressure by LLINs and IRS has favoured species and strains able to evade interventions by biting and resting outdoors, and finding refuge in animal hosts. Of further concern is the expansion of *Anopheles stephensi* vectors into the Horn of Africa. This invasive species is already established in Djibouti (Sinka 2020), and is expanding into Ethiopia (Carter 2021), where refugees displaced by armed conflict north of the country might be particularly vulnerable to new outbreaks. *An stephensi* is unlikely to be effectively controlled with LLINs or IRS; the species thrives in urban environments, breeds easily in containers, and displays a high degree of behavioural plasticity.

Description of the intervention

Personal protective measures that effectively prevent mosquito bites, irrespective of place and time, may address current control gaps and complement existing interventions (Killeen 2014). Among these measures, topical repellents are a particularly attractive candidate, given extensive data on their safety and efficacy at reducing mosquito bites. Furthermore, topical repellents can be distributed easily among susceptible populations through co-operation with the private sector. As an intervention tool, repellents may be particularly useful for high-risk groups who have increased behavioral or occupational exposure to malaria vectors, and who are not as likely to be protected by LLIN or IRS. These groups include refugees (Rowland 2001), miners (Olapeju 2021), forest-goers, soldiers, or indigenous groups (Bevilacqua 2015), among others who play an important role in maintaining, increasing, and spreading malaria transmission.

Topical repellents include any substance that is directly applied to the skin to prevent insect bites. They represent one of the most widely-used forms of vector control throughout human history (Herodotus 1996). They are commonly available as lotions, sprays or gels, but can also be found in the form of soaps that leave a repellent residue on the skin (Kroeger 1997; Rowland 2004). Oils derived from plants such as citronella (*Cymbopogon*), neem (*Azidarachta indica*), and eucalyptus (*Eucalyptus maculate citriodon*) have been used since antiquity for this purpose, alone or combined with petroleum jelly and similar preparations (Maia 2011). The development of modern repellents began during the 1950s. Of these, N,N-diethyl-m-toluamide (DEET) is the most widely used. Other common compounds include: 2-2-hydroxyethyl-1-piperidinecarboxylic (icaridin, or picaridin in the USA), para-menthane-3,8-diol (PMD), and 3-(N-butyl-N-acetyl)-aminopropionic acid ethyl ester (IR3535).

Topical repellents are already widely recommended for tourists and expatriates working in malaria-endemic settings (WHO 2020b). However, it is unclear if the programmatic integration of repellents as an additional vector control commodity into existing control programs in endemic areas would result in fewer malaria cases. Furthermore, there are important drawbacks that may influence the programmatic usefulness of repellents. Firstly, topical repellents do not kill mosquitoes: they offer personal protection by preventing mosquito bites. Because mosquitoes are not killed, they may be diverted from individuals who use repellents to those who do not (Maia 2013). This raises health equity implications, as accessibility to these products may vary across the different societal strata. Secondly, their effect is short-lived and requires repeated administrations. Therefore, protection is highly dependent on the user's regular compliance (Sangoro 2014). While

repellents are usually well-received by communities (Sangoro 2014), their regular and adequate use has been shown to be poor, even in trial settings where engagement is enhanced (Sluydst 2016). In some communities many of the perceived benefits of repellents derive from non-prescribed uses, such as applying them directly to insects or bed nets (Gryseels 2015). Finally, the large-scale distribution of topical repellents entails further costs to already under-funded control programs, with an estimated incremental cost-effectiveness ratio (ICER) ranging between USD 212 and USD 832 per infection averted (Agius 2020).

How the intervention might work

Topical repellents do not kill mosquitoes but prevent mosquito bites by interfering with mosquitoes' olfactory reception, affecting their ability to locate and feed on a treated host. The mode of action involves complex interactions between repellent compounds and the olfactory receptors (OR) and gustatory receptors (GR) of haematophagous insects. While the exact mechanism is unclear, DEET, IR3535, and citronella appear to act as allosteric agonistic and antagonistic modulators on several ORs, hampering the mosquito's navigation to its blood meal. Similarly, these compounds have been shown to stimulate chemoreceptors in the feeding apparatus of mosquitoes, acting as deterrents upon contact. Therefore, the effect on ORs could prevent mosquitoes from landing on treated hosts, while stimulation of the GRs would lead less volatile compounds to act as contact repellents or irritants (Dickens 2013).

Malaria transmission is dependent on vectorial capacity. This is a concept coined during the first Global Malaria Eradication Campaign, and can be understood as the daily rate at which parasites are inoculated to susceptible hosts from an originally infective case, if all mosquitoes biting that case become infected (Garrett-Jones 1964). This parameter, therefore, evaluates mosquitoes' capacity to transmit malaria, irrespective of parasite densities in a population. Among the key determinants of vectorial capacity is the probability of a mosquito biting a person, which has an exponential effect on the number of new infections. Topical repellents reduce this probability at an individual level by reducing contact between treated people and mosquitoes. However, because vectors may be diverted from treated to untreated individuals there is a possibility of increased transmission among unprotected or non-compliant groups, potentially leading to loss of effectiveness at a population level. Nevertheless, they may be useful to prevent malaria transmission among high-risk groups, in which LLINs, IRS, and other traditional vector control interventions are unfeasible, and where effectively covering the entire susceptible population is not possible.

Why it is important to do this review

The incorporation of LLINs into malaria control programmes is accountable for around 68% of the 660 million cases averted between 2000 and 2015 (Bhatt 2015). However, the recent stagnation in progress highlights the need to develop new complementary interventions that address the gap that bed nets fail to cover. This is particularly true in non-African settings, where the main vectors of the disease often feed outdoors and early in the evening, or can take blood meals from animals, as well as humans. It is widely accepted that complementary interventions will be required, if elimination is to be achieved. Citing the WHO Director General: "If we continue with a 'business as usual approach' – employing the same level of resources and the same interventions – we will face near-certain increases in malaria cases and deaths" (WHO 2020a).

In Africa, high coverage of LLINs and IRS programs has been linked to changes in mosquito behaviour, allowing these to preclude control by programmes based on intra-domiciliary interventions like these (Russell 2011). Afro-tropical malaria vectors of the main species complexes, *An gambiae s.l.* and *An funestus s.l.*, can change their feeding behaviours, biting people before they go to bed (and are protected by LLINs) (Ferreira 2017). In some cases, traditional vectors that would normally bite during the late evening hours and indoors have been drastically reduced by LLINs and IRS, but replaced with relatively less efficient, yet highly adaptable species, such as *An arabiensis* (Killeen 2017). Such species, presenting with a high degree of behavioural plasticity, are a challenge as their adaptability creates gaps in control strategies. It is hypothesized that topical repellents may partially cover the gaps of LLINs and IRS by protecting individuals outdoors, before they go to bed. They are also unaffected by insecticide resistance, given their different mechanism of action. There is, however, a lack of clear evidence to support this.

This Cochrane Review aims to measure the effectiveness of topical repellents, alone or in combination with LLINs and other background interventions, in reducing the risk of malaria infection among high-risk and non-high-risk populations in endemic regions. Furthermore, this can be framed within the United Nations Sustainable Development Goal (SDG) 3: Good health and well-being, which presents both a global reduction of maternal and child mortality, and the end of the malaria epidemic, as targets to meet by 2030 (WHO 2020a).

OBJECTIVES

To assess the effect of topical repellents alone or in combination with other background interventions for reducing malaria incidence in high-risk and non-high-risk populations living in endemic areas.

METHODS

Criteria for considering studies for this review

Types of studies

We will include both randomized and non-randomized controlled studies.

Randomized studies

We will include studies randomized at either the cluster or individual level, including:

- randomized controlled trials (RCTs);
- cluster-randomized controlled trials (cRCTs) with at least two clusters per arm;
- cluster-randomized cross-over studies with at least three data points both before and after the intervention is introduced; and
- cluster-randomized studies using a stepped-wedge approach.

Non-randomized studies

We will also include non-randomized studies that meet our inclusion criteria. However, we will assess these studies separately in a secondary analysis of observational studies for adverse effects

and any summary estimates of effectiveness. We are including non-randomized studies because we expect to find a limited number of randomized studies addressing the research question, and aim to synthesize the best available evidence. We will include:

- controlled before-after studies (CBA) with baseline data, a contemporaneous control group, and at least two sites per arm, if the study has ruled out any significant baseline imbalances;
- controlled interrupted time series (ITS) with at least three data points before and after the intervention was introduced;
- non-randomized controlled cross-over trials with a clearly defined time point for when the cross-over occurred, and monitoring of at least two transmission seasons before and after the cross-over.

We will assess the methodological quality of each observational study design according to EPOC (Effective Practice and Organisation of Care) criteria for inclusion EPOC 2017. For studies that meet the EPOC criteria, we will use the ROBINS-I signalling questions to assess their risk of bias (Sterne 2016). If the studies are not at critical risk of bias, we will extract study characteristics as per protocol and summarize data on effectiveness and adverse events in a tabular form.

Types of participants

Eligible participants are children and adults resident in a malaria-endemic area, categorized into high-risk or non-high-risk populations. For the purpose of this review, we will consider high-risk populations to be populations who either do not have access to, or are less likely to benefit from, programmatic vector control interventions (IRS and LLINs). Examples of these groups include, but are not limited to, refugees, miners, forest-goers, soldiers, or indigenous groups.

Types of interventions

We will include trials with or without background interventions (LLINs, IRS, or other), as long as they are balanced between trial arms.

Intervention

The interventions of interest are topical repellents, including DEET, icaridin, picaridin, IR3535, para-menthane-3,8- diol (PMD), oil of lemon eucalyptus (OLE), or 2-undecanone (methyl nonyl keton).

Control

Individuals in eligible control groups will receive a placebo or no treatment.

We will exclude data of participants infected with *P vivax* or *P ovale* from trials carried out in endemic areas for these parasites if these participants had not been screened and cleared of parasites at the beginning of the trial. This is to prevent the inclusion of recrudescent cases in the analysis, since these cannot be prevented by topical repellents. Participants who received radical cure with a 8-aminoquinoline (such as primaquine), and a schizonticidal drug (such as chloroquine), will be considered to be clear of latent infection, following WHO guidelines (WHO 2021).

Types of outcome measures

Primary outcomes

- Malaria case incidence: new cases of clinical malaria (caused by *Plasmodium* spp.) confirmed through blood smears or mRDTs
- Malaria infection incidence: new *Plasmodium* spp. infections confirmed through thick or thin blood smears, mRDTs, or polymerase chain reaction (PCR)

Secondary outcomes

- Incidence of recorded adverse events (including skin irritation, local pain, eye irritation, irritation of upper airways, nausea, vomiting, headaches, dizziness or confusion, allergic or anaphylactic reactions, and systemic toxicity)
- Malaria prevalence
- Anaemia (haemoglobin < 8 g/dL)
- Time to first infection (days)
- All-cause fever
- Incidence of severe malaria
- Malaria-related mortality
- Adherence to regular usage of the intervention (defined based on recommendations provided by researchers to participants of individual trials)
- Human biting rate (HBR)
- Entomological inoculation rate (EIR)
- Sporozoite rate (SR)
- Human blood index (HBI)

Search methods for identification of studies

We will attempt to identify all relevant trials, regardless of language or publication status. We will add these as new studies (published, unpublished, in press, and ongoing) to the previous list of included studies on topical repellents for malaria prevention (Maia 2018).

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;
- LILACS (Latin American and Caribbean Health Science Information database); and
- the French Institute of Research for Development's Horizon Pleins Textes database.

We will also search the WHO International Clinical Trials Registry Platform and the meta-Register of Controlled Trials (mRCT), using the search terms: mosquito*, malaria, DEET, PMD, IR3535, Icaridin, Picaridin, topical and repellent*.

Searching other resources

Conference proceedings

We will search the following conference proceedings for relevant abstracts:

- Multilateral Initiative on Malaria (MIM) conference abstract booklets;
- Annual American Society of Tropical Medicine and Hygiene (ASTMH) conference;
- Entomological Society of America; and
- Society of Vector Ecology of America.

Organizations and pharmaceutical companies

We will contact several organizations for ongoing and unpublished trials, including: the WHO, Centers for Disease Control and Prevention (CDC), United States Agency for International Development (USAID), US Armed Forces Pest Management Board (AFPMB), Deployed War Fighter Protection Program (DWFP), London School of Hygiene and Tropical Medicine (LSHTM), Liverpool School of Tropical Medicine (LSTM), and chemical companies including Bayer, Badische Anilin- und Sodafabrik (BASF), SC Johnson, Mosiguard, and other local companies.

Reference lists

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

Data collection and analysis

Selection of studies

Two review authors (MGW and JCGF) will independently assess the titles and abstracts of trials identified by the searches. The same review authors will assess full-text copies of potentially relevant trials for inclusion using an eligibility form based on the inclusion criteria. We will compare included trials, and resolve any disagreements by discussion and consensus, with arbitration by the third review author (MFM) 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

Two review authors (MGW and JCGF) will independently extract information from the trials using pre-piloted, electronic data extraction forms. In case of differences in extracted data, the two review authors will discuss these differences to reach consensus. If unresolved, further discussion will involve the third author (MFM). In case of missing data, we will contact the original trial author(s) for clarification.

For all eligible studies 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 (in the case of cRCTs); sample size; method of blinding of participants and personnel; diagnostic method; method used for ascertainment of adherence; primary vector; vector biting time; vector biting preference; malaria endemicity (prevalence); presence of different *Plasmodium* species; clearance of *P vivax* and *P ovale* parasites at start.
2. Participants: trial settings, population characteristics, whether participants are considered a high-risk population or not, and if such, in which category they would fit (for example: displaced populations, such as refugees, forest goers, or deployed military); whether participants are likely to have had no previous exposure to malaria (for example: displaced populations, deployed troops, or other); 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.
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 participants experiencing each outcome and the number of participants in each treatment group. For count data outcomes, we will extract the number of outcomes in the treatment and control groups, 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 analyzed; measure of effect (such as risk ratio, odds ratio, or mean difference) with confidence intervals (CI) or standard deviations; number of participants; and the intracluster correlation coefficient (ICC) value.

Other studies

For non-randomized studies that we consider to be eligible for inclusion according to EPOC criteria EPOC 2017, and do not consider to be at critical risk of bias Sterne 2016, we will extract data on estimates of effectiveness and adverse events.

Assessment of risk of bias in included studies

We will quantify the effect of assignment to the interventions, regardless of whether the interventions were adhered to as intended (the 'intention-to-treat' effect).

Randomized studies

Two review authors (MGW and JCGF) will independently assess risk of bias using the Cochrane risk of bias tool version two (RoB 2), which is a revised tool to assess the risk of bias in randomized trials (Higgins 2021a; Sterne 2019).

We will assess the primary outcomes and incidence of adverse events for risk of bias.

The two review authors (MGW and JCGF) will resolve any discrepancies through discussion or by consulting the third review author (MFM). We will assess the risk of bias according to the following domains (Higgins 2021b):

1. bias arising from the randomization process;
2. bias due to deviations from intended interventions;
3. bias due to missing outcome data;
4. bias in measurement of the outcome; and
5. bias in the selection of the reported result.

For each domain, we will answer the signalling questions to elicit information for an assessment of the risk of bias. We will use the answers to the signalling questions to assess the domain level judgements of risk of bias as 'low risk of bias', 'some concerns', or 'high risk of bias'. We will summarize the risk of bias judgements for each of the domains listed across different studies. The overall judgement of risk of bias will depend on each of the domain-level judgements.

For cluster-randomized clinical trials, we will add RoB 2 Domain 1b, 'Bias arising from the timing of identification and recruitment of participants' with its corresponding signalling questions, in order to assess identification/recruitment bias (Higgins 2021c).

We will use the risk of bias Excel tool (available from: www.riskofbias.info/), and make a summary of the risk of bias by each outcome within and across studies (Higgins 2021b).

Non-randomized studies

For non-randomized studies of interventions (NRSI), two review authors (MGW and JCGF) will independently assess risk of bias using the ROBINS-I tool (Sterne 2016). For each outcome, we will answer signalling questions to systematically judge the risk of bias and provide the basis for an overall risk of bias judgement. The signalling questions will assess bias according to seven different domains:

1. bias due to confounding;
2. bias in selection of participants into the study;
3. bias in classification of interventions;
4. bias due to deviations from intended interventions;
5. bias due to missing data;
6. bias in measurement of outcomes; and
7. bias in selection of the reported result.

Domains one and two cover bias pre-intervention, the third domain is bias at the stage of intervention, and domains four to seven represent bias postintervention.

We will judge the risk of bias to be 'low', 'moderate', 'serious' or 'critical'. 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; we will exclude studies at critical risk of bias, and neither extract nor discuss their data.

Confounding domains

- Socioeconomic status: lower socioeconomic status is considered a prognostic factor for increased risk of malaria transmission.
- Geographical location: malaria transmission is heterogenous across different geographical regions and can therefore be a predictor of malaria risk.

In the review, we will present risk of bias assessments for RCTs and NRSI using outcome-level traffic light plots created using the Robvis tool for ROBINS-I (McGuinness 2020).

Measures of treatment effect

We will compare intervention and control data using risk ratios, rate ratios, or hazard ratios presented with their associated 95% confidence intervals (CIs).

Unit of analysis issues

We will combine results from cRCTs with individual RCTs if they have adjusted for clustering in their analysis, and will present results using forest plots. If there was no adjustment for clustering in the cRCTs, we will attempt to adjust data before combining it with data from individually-randomized RCTs. We will attempt to adjust the data by multiplying standard errors by the square root of the design effect (Higgins 2021c). If the trial does not report the ICC value, 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 their 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 an intention-to-treat analysis by analyzing all recruited participants in the group to which they were randomized at the start.

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% and 60%; substantial if they are between 61% and 75%; and considerable if they are between 76% and 100%. We will regard a Chi^2 test statistic with a P value ≤ 0.10 to indicate 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 reasons for asymmetry.

Data synthesis

We will group trials and analyze them by *Plasmodium* spp. infection incidence and *Plasmodium* spp. case incidence. Within each group, we will stratify by whether LLINs were included in both intervention and control groups, and by whether or not we considered the participants to be a high-risk population in both intervention and control groups. We will analyse data using Review Manager 2020 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 a fixed-effect or random-effects model based on the consideration of clinical and methodological heterogeneity between trials, as described previously.

Data from eligibile non-randomized studies on estimates of effectiveness and adverse events will be presented in narrative form.

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. evaluate malaria infection incidence and malaria case incidence in studies that investigated the topical repellent with/without LLINs or IRS;
2. evaluate malaria infection incidence and malaria case incidence in studies with/without high-risk populations, including migrants, refugees, travellers, miners, forest goers, deployed troops, and other mobile or displaced populations.

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

For the primary outcome, we will perform the following sensitivity analyses and compare each against the overall result:

1. exclusion of trials at high risk of bias;
2. exclusion of cRCTs;
3. exclusion of trials that were not placebo-controlled;
4. for cRCTs with an estimated ICC, the impact of varying the ICC; and
5. the impact of adherence (i.e. including only participants who reported that they adhered', as compared to our primary ITT analysis, which assumes that all participants adhered equally to the intervention).

Summary of findings and assessment of the certainty of the evidence

We will assess the certainty of the evidence for each primary outcome and the incidence of adverse events using the GRADE approach (Guyatt 2011), 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.
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-certainty 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 were observed (Balshem 2011). NRSI assessed with the ROBINS-I tool, which covers the risk of bias due to lack of randomization, will also start as high-certainty evidence. We will summarize our findings in a summary of findings table.

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APPENDICES

Appendix 1. Detailed search strategy for MEDLINE (OVID)

Ovid MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations (1946 to present)

1	Malaria/
2	malaria.tw.
3	1 or 2
4	Insect Vectors/
5	vector*.tw.
6	mosquito*.mp. or Mosquito Vectors/
7	Anopheles/ or anopheles.tw.
8	Insect Bites/ and Stings
9	4 or 5 or 6 or 7 or 8
10	3 and 9
11	Mosquito Control/
12	10 or 11
13	Insect Repellents/
14	topical repel*.tw.
15	repellent*.tw.
16	(lotion* or gel or gels or roll-on* or wipe* or soap* or cream*).tw.
17	(Spray* and skin).mp.
18	personal protection.mp.
19	13 or 14 or 15 or 16 or 17 or 18
20	12 and 19
21	randomized controlled trial/
22	Controlled Clinical Trial/
23	(randomized or placebo or randomly or trial or groups).tw.
24	Interrupted Time Series Analysis/
25	Controlled Before-After Studies/
26	Cross-Over Studies/
27	21 or 22 or 23 or 24 or 25 or 26
28	20 and 27

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All authors contributed to the design and drafting of the protocol (MWG, JCGF, MFM).

All authors read and approved the final protocol version.

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MGW has no known conflicts of interest.

JCGF has no known conflicts of interest.

MFM has no known conflicts of interest.

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