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Topical repellents for malaria prevention (Review)

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TABLE OF CONTENTS

| | |
|--|----|
| ABSTRACT | 1 |
| PLAIN LANGUAGE SUMMARY | 2 |
| SUMMARY OF FINDINGS | 4 |
| BACKGROUND | 6 |
| OBJECTIVES | 8 |
| METHODS | 8 |
| RESULTS | 11 |
| Figure 1. | 12 |
| DISCUSSION | 15 |
| AUTHORS' CONCLUSIONS | 17 |
| ACKNOWLEDGEMENTS | 18 |
| REFERENCES | 19 |
| CHARACTERISTICS OF STUDIES | 23 |
| RISK OF BIAS | 32 |
| DATA AND ANALYSES | 33 |
| Analysis 1.1. Comparison 1: Topical repellents versus placebo or no intervention, Outcome 1: Malaria incidence (case and infection) | 34 |
| Analysis 1.2. Comparison 1: Topical repellents versus placebo or no intervention, Outcome 2: Malaria incidence (use of other interventions) | 35 |
| Analysis 1.3. Comparison 1: Topical repellents versus placebo or no intervention, Outcome 3: Malaria incidence (by risk population) | 35 |
| Analysis 1.4. Comparison 1: Topical repellents versus placebo or no intervention, Outcome 4: Reported adverse events in the topical repellents arm of included studies | 35 |
| Analysis 1.5. Comparison 1: Topical repellents versus placebo or no intervention, Outcome 5: Malaria prevalence | 36 |
| Analysis 1.6. Comparison 1: Topical repellents versus placebo or no intervention, Outcome 6: Malaria prevalence (per-protocol analysis) | 36 |
| Analysis 1.7. Comparison 1: Topical repellents versus placebo or no intervention, Outcome 7: Anaemia | 37 |
| Analysis 1.8. Comparison 1: Topical repellents versus placebo or no intervention, Outcome 8: All-cause fever | 37 |
| Analysis 1.9. Comparison 1: Topical repellents versus placebo or no intervention, Outcome 9: Adherence to the intervention .. | 37 |
| ADDITIONAL TABLES | 37 |
| APPENDICES | 38 |
| HISTORY | 41 |
| CONTRIBUTIONS OF AUTHORS | 41 |
| DECLARATIONS OF INTEREST | 41 |
| SOURCES OF SUPPORT | 42 |
| DIFFERENCES BETWEEN PROTOCOL AND REVIEW | 42 |
| INDEX TERMS | 42 |

[Intervention Review]

Topical repellents for malaria prevention

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ABSTRACT

Background

Insecticide-based interventions, such as long-lasting insecticide-treated nets (LLINs) and indoor residual spraying (IRS), remain the backbone of malaria vector control. These interventions target mosquitoes that prefer to feed and rest indoors, but have limited capacity to prevent transmission that occurs outdoors or outside regular sleeping hours. In low-endemicity areas, malaria elimination will require that these control gaps are addressed, and complementary tools are found. The use of topical repellents may be particularly useful for populations who may not benefit from programmatic malaria control measures, such as refugees, the military, or forest goers. This Cochrane Review aims to measure the effectiveness of topical repellents to prevent malaria infection among high- and non-high-risk populations living in malaria-endemic regions.

Objectives

To assess the effect of topical repellents alone or in combination with other background interventions (long-lasting insecticide-treated nets, or indoor residual spraying, or both) for reducing the incidence of malaria in high- and non-high-risk populations living in endemic areas.

Search methods

We searched the following databases up to 11 January 2023: the Cochrane Infectious Diseases Group Specialised Register; CENTRAL (in the Cochrane Library); MEDLINE; Embase; CAB Abstracts; and LILACS. We also searched trial registration platforms and conference proceedings; and contacted organizations and companies for ongoing and unpublished trials.

Selection criteria

We included randomized controlled trials (RCTs) and cluster-randomized controlled trials (cRCTs) of topical repellents proven to repel mosquitoes. We also included non-randomized studies that complied with pre-specified inclusion criteria: controlled before-after studies (CBA), controlled interrupted time series (ITS), and controlled cross-over trials.

Data collection and analysis

Four review authors independently assessed trials for inclusion, and extracted the data. Two authors independently assessed the risk of bias (RoB) using the Cochrane RoB 2 tool. A fifth review author resolved any disagreements. We analysed data by conducting a meta-analysis, stratified by whether studies included populations considered to be at high-risk of developing malaria infection (for example, refugees, forest goers, or deployed military troops). We combined results from cRCTs with RCTs by adjusting for clustering and presented

Topical repellents for malaria prevention (Review)

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results using forest plots. We used the GRADE framework to assess the certainty of the evidence. We only included data on *Plasmodium falciparum* infections in the meta-analysis.

Main results

Thirteen articles relating to eight trials met the inclusion criteria and were qualitatively described. We included six trials in the meta-analysis (five cRCTs and one RCT).

Effect on malaria incidence

Topical repellents may slightly reduce *P falciparum* infection and clinical incidence when both outcomes are considered together (incidence rate ratio (IRR) 0.74, 95% confidence interval (CI) 0.56 to 0.98; 3 cRCTs and 1 RCT, 61,651 participants; low-certainty evidence); but not when these two outcomes were considered independently. Two cRCTs and one RCT (12,813 participants) evaluated the effect of topical repellents on infection incidence (IRR 0.76, 95% CI 0.56 to 1.02; low-certainty evidence). One cRCT (48,838 participants) evaluated their effect on clinical case incidence (IRR 0.66, 95% CI 0.32 to 1.36; low-certainty evidence). Three studies (2 cRCTs and 1 RCT) included participants belonging to groups considered at high-risk of being infected, while only one cRCT did not include participants at high risk.

Adverse events

Topical repellents are considered safe. The prevalence of adverse events among participants who used topical repellents was very low (0.6%, 283/47,515) and limited to mild skin reactions.

Effect on malaria prevalence

Topical repellents may slightly reduce *P falciparum* prevalence (odds ratio (OR) 0.81, 95% CI 0.67 to 0.97; 3 cRCTs and 1 RCT; 55,366 participants; low-certainty evidence). Two of these studies (1 cRCT and 1 RCT) were carried out in refugee camps, and included exclusively high-risk populations that were not receiving any other background vector control intervention.

Authors' conclusions

There is insufficient evidence to conclude that topical repellents can prevent malaria in settings where other vector control interventions are in place. We found the certainty of evidence for all outcomes to be low, primarily due to the risk of bias. A protective effect was suggested among high-risk populations, specially refugees, who might not have access to other standard vector control measures.

More adequately powered clinical trials carried out in refugee camps could provide further information on the potential benefit of topical repellents in this setting. Individually randomized studies are also likely necessary to understand whether topical repellents have an effect on personal protection, and the degree to which diversion to non-protected participants affects overall transmission dynamics.

Despite this, the potential additional benefits of topical repellents are most likely limited in contexts where other interventions are available.

PLAIN LANGUAGE SUMMARY

What are the benefits and risks of using topical insect repellents to prevent malaria?

Key messages

- Topical repellents may slightly reduce the incidence and prevalence of malaria caused by *Plasmodium falciparum*.
- These changes seem to be particularly important in high-risk populations, specifically in refugees living in camps where there are fewer other options.
- Topical repellents may make little or no difference in malaria prevalence and incidence in settings where insecticide-treated nets, and other options to control the transmission of malaria are readily available.

What is malaria?

Malaria is a disease caused by at least five species of parasites from the genus *Plasmodium*, and spread by the bite of *Anopheles* mosquitoes. The disease regularly affects people in tropical areas of Central and South America, South and Southeast Asia, and particularly, Africa. Over 247 million malaria cases and 619,000 deaths occurred in 2021, mostly in Africa. The disease affects the function of red blood cells, which transport oxygen through the body. This generally causes fever, malaise (a feeling of 'just not feeling well'), and other mild symptoms. However, some people can develop complicated disease, which is associated with a severe reduction in the number of circulating red blood cells, and problems in the liver, brain, and other organs.

Malaria can be treated with different medicines, which are generally effective. Certain tools that prevent mosquito bites, like nets treated with insecticides, can protect people from getting it, and have helped to significantly reduce the number of cases around the world.

Nonetheless, most of these approaches target mosquitoes that feed indoors and on humans. They are less effective against species that can feed outdoors, so do not really eliminate the disease.

What did we want to find out?

The aim of this Cochrane Review was to find out if topical insect repellents (substances applied to the skin to prevent mosquito bites) can prevent malaria in people living in regions where this disease occurs regularly. We were particularly interested in their effect on people who might not be adequately protected by other measures, which are more commonly used to prevent malaria.

We wanted to find out if topical repellents were better than a placebo, or no intervention at all, to reduce two indicators of malaria transmission:

- Malaria incidence (the number of new cases in a period of time);
- Malaria prevalence (the number of all cases at a certain moment).

We also wanted to know if topical repellents caused any adverse side effects to people who used them.

What did we do?

We searched the existing literature for studies that compared the effect of topical repellents (alone or in combination with other tools to prevent mosquito bites) with a placebo or no intervention. We compared and summarized the results of the included studies, and rated our confidence in the evidence they provided, based on the methods used in each one.

What did we find?

We included a total of eight studies, which included over 60,000 people. The studies took place in areas with low malaria transmission, mostly in Southeast Asia and South America.

The topical repellents evaluated included lotions, soaps, and cosmetics. We found evidence suggesting that topical repellents may slightly reduce the incidence and prevalence of malaria cases caused by *P falciparum* in settings where other tools to prevent mosquito bites are not available. Despite this, our findings suggest that repellents probably make little or no difference in places where these tools are already widely used. Topical repellents are considered safe, and the prevalence of adverse side effects was very low.

What are the limitations of the evidence?

The benefits of topical repellents were particularly clear among refugees. However, shortfalls in the design of the included studies did not allow us to generalize these observations to other contexts. We only included cases of malaria caused by the parasite *P falciparum*. We also recognize that studies measured and reported adherence differently, and often did not know if the participants actually used the repellent as advised.

How up to date is this review?

The evidence is up to date to 11 January 2023.

SUMMARY OF FINDINGS

Summary of findings 1. Topical repellents versus placebo or no treatment in adults and children living in malaria-endemic areas

Patient or population: adults and children in malaria-endemic areas

Setting: malaria-endemic areas (November 1991 to June 2016; Bolivia, Cambodia, Ecuador, Laos PDR, Myanmar, Pakistan, Peru, Tanzania, Thailand)

Intervention: topical repellents

Comparison: placebo or no treatment

| Outcome | Anticipated absolute effects (95% CI) | | Relative effect (95% CI) | N° of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|--|---|-----------------------------------|------------------------------|-----------------------------------|--|
| | Risk with placebo or no treatment | Risk difference with topical repellents | | | | |
| Malaria infection incidence alone (Follow-up: mean 6 months) | 37 per 1000 | 9 fewer per 1000 (16 fewer to 1 more) | Rate ratio 0.76 (0.56 to 1.02) | 12,813 (2 cRCTs, 1 RCT) | ⊕⊕○○ Low ^{a,b} | Topical repellents may make little or no difference to the incidence of <i>P falciparum</i> infection. |
| Malaria case incidence alone (Follow-up: mean 12 months) | 22 per 1000 | 7 fewer per 1000 (15 fewer to 8 more) | Rate ratio 0.66 (0.32 to 1.36) | 48,838 (1 cRCT) | ⊕⊕○○ Low ^{c,d} | Topical repellents may make little or no difference to <i>P falciparum</i> clinical case incidence |
| Malaria case and infection incidence together (Follow-up: mean 7 months) | 24 per 1000 | 6 fewer per 1000 (10 fewer to 0 fewer) | Rate ratio 0.74 (0.56 to 0.98) | 61,651 (3 cRCTs, 1 RCT) | ⊕⊕○○ Low ^{b,e} | Topical repellents may slightly reduce <i>P falciparum</i> infection and clinical case incidence when both outcomes are pooled |
| Adverse events Assessed with self-reported questionnaires and in-person interviews (Follow-up: mean 13 months) | A total of 283 adverse events (0.6%) were observed among participants who received topical repellents. | | | 47,515 (6 cRCTs, 1 RCT) | - | Topical repellents are considered safe |
| Malaria prevalence (Follow-up: mean 13 months) | 13 per 1000 | 2 fewer per 1000 (4 fewer to 0 fewer) | Odds ratio 0.81 (0.67 to 0.97) | 55,366 (3 cRCTs, 1 RCT) | ⊕⊕○○ Low ^{b,f} | Topical repellents may slightly reduce <i>P falciparum</i> prevalence |

Abbreviations: CI: confidence interval; cRCT: cluster-randomized controlled trial; RCT: randomized controlled trial.

The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). The denominator in the malaria incidence outcomes is person-years, and people in the prevalence outcome.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

^aDowngraded 1 level due to risk of bias associated with the procedures used to randomize participants, conceal allocation, and imbalances in the allocation groups.

^bDowngraded 1 level due to indirectness associated with the inclusion of only pregnant women in one study.

^cDowngraded 1 level due to risk of bias associated with imbalances in the allocation groups and the lack of placebo in controls.

^dDowngraded 1 level due to imprecision, as 95% CIs include a relevant reduction in malaria incidence and no effect.

^eDowngraded 1 level due to risk of bias associated with procedures used to conceal allocation, imbalances in the allocation groups, and a large proportion of losses to follow-up (16.6%) in one study.

^fDowngraded 1 level due to risk of bias associated with the step-wedged design and the lack of placebo in the control group of two studies, issues in the procedures used to blind study participants, and imbalances in allocation groups.

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: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae*, and *Plasmodium knowlesi*. Over 247 million cases of malaria were estimated to have occurred in 2021, increasing from 245 million the previous year, most of them in Africa (WHO 2022).

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 (Sinka 2012). Malaria has a wide clinical presentation, with most cases characterized by the presence of mild non-specific 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 result in severe disease and death, if untreated. In 2021, 619,000 people were estimated to have died of malaria, most of them in Africa (WHO 2022). 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 Southeast Asia, and is also often associated with complications that include acute kidney disease and hyperparasitaemia. Infections with *P vivax*, *P ovale*, and *P malariae* are 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, treatment, and diagnostic measures. These measures include long-lasting insecticide-treated nets (LLINs), artemisinin-based combination therapies (ACTs), and inexpensive, easily scalable rapid diagnostic tests (RDTs). The addition of these interventions to existing strategies, such as indoor residual spraying (IRS) 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 over the last six years. The World Health Organization (WHO) 2016 to 2030 Global Technical Strategy for Malaria presented the ambitious goal of reducing global incidence by 40% in 2020, and by 90% in 2030, compared to 2015 figures (WHO 2015). The world remains off-track to meet this target, with a global incidence reduction of less than 2% between 2015 and 2019, and an increase of 2 million cases in 2021, compared to the previous year (WHO 2022). This regression is attributed to several factors, including poor access to health systems, political unrest, poor government commitment to malaria control, reduced effectiveness of traditional chemical-based interventions, and disruption in health services caused by the COVID-19 pandemic (WHO 2022). 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 IRS, are the backbone of current malaria vector control. In settings where pyrethroid resistance is established, these interventions are thought to remain partially effective at reducing transmission (Kleinschmidt 2018),

through their physical barrier and associated sublethal effects (Unwin 2023). However, their effectiveness in reducing malaria transmission depends on adequate coverage. Furthermore, these interventions predominantly target mosquito species that feed mostly indoors, on humans (Killeen 2014). While LLINs and IRS have been highly effective in most African settings, 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). For instance, this is the case in forested regions within the Greater Mekong Subregion in Southeast Asia, where outdoor malaria transmission by exophilic vectors represents a major challenge in the elimination of the disease (Chaumeau 2022; Durnez 2013); and likely influences transmission among gold miners in South America (Douine 2020). Interventions targeting outdoor malaria transmission are still considered an unmet public health need (WHO 2023a)

Another important concern is the persistence of residual malaria transmission, whereby malaria elimination cannot be achieved despite optimal coverage of effective interventions (Killeen 2014). Selection by LLINs and IRS has favoured species and strains with pre-existing traits that limit the efficacy of these interventions, such as biting and resting outdoors, or feeding on animal hosts (Govella 2013; Killeen 2014). The expansion of *Anopheles stephensi* into the Horn of Africa leads to further concerns. This invasive species is already established in Djibouti (Sinka 2020), and is expanding through Ethiopia (Carter 2021), where refugees displaced by armed conflict north of the country might be particularly vulnerable to new outbreaks. It has also been detected in Sudan, Somalia, Nigeria (WHO 2022), and Kenya (Ochomo 2023). The efficacy of existing vector control strategies to curb the expansion of this vector in African settings remains unknown.

Description of the intervention

Personal protective measures that effectively prevent mosquito bites, regardless 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 (Alpern 2016; Nguyen 2023). Topical repellents can be distributed easily among susceptible populations through co-operation with the private sector and local governments. As an intervention tool, repellents may be particularly useful for high-risk groups who have increased behavioural or occupational exposure to malaria vectors, and who are not as likely to be protected by either LLINs or IRS. These groups include refugees (Rowland 2001), miners (Olapaju 2021), forest-goers, soldiers, or indigenous groups (Bevilacqua 2015), among others, who play an important role in maintaining malaria transmission.

Topical repellents include any substance that is applied directly 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 (*Azadirachta 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

Topical repellents for malaria prevention (Review)

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). Commonly commercially available formulations include: DEET (5% to 100%), picaridin (7% to 20%), IR3535 (7.5% to 19.7%), oil of lemon eucalyptus (10% to 40%), citronella oil (0.5% to 20%), catnip oil (7% to 15%), and 2-undecanone (1% to 2% (Nguyen 2023)).

Topical repellents are already regularly used by tourists and expatriates working in malaria-endemic settings, and their use has been proposed as an alternative to prevent malaria in these and other groups in which LLINs and IRS are expected to be less effective (WHO 2023b). Despite this, it is unclear if the programmatic integration of repellents as an additional vector control commodity into existing control programmes in endemic areas will result in fewer malaria cases (WHO 2023b). There are important drawbacks that may influence the programmatic usefulness of repellents. First, topical repellents do not kill mosquitoes, they offer 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. Second, their effect is short-lived and requires repeated administrations. Therefore, protection is highly dependent on user 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 (Sluydts 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 programmes, 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 bites by interfering with their olfaction, affecting their ability to locate and feed on a treated host. The mode of action involves complex interactions between repellent compounds and the olfactory and gustatory receptors of haematophagous insects (Dickens 2013). While the exact mechanism is unclear, DEET, the most thoroughly studied repellent, appears to act by activating and inhibiting several olfactory receptors, interfering with the mosquito's capacity to detect airborne molecules, while simultaneously triggering avoidance behaviours (Norris 2017). IR3535 and picaridin are thought to act similarly (Norris 2017). These compounds have also been shown to stimulate other receptors in the feeding apparatus of mosquitoes, acting as deterrents upon contact (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 original infective case, assuming all mosquitoes biting it become infected (Garrett-Jones 1964). 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. Recent updates to the classical model have also incorporated changes to

the mosquito biting rate, which not only reduces the probability of infection, but also impacts the number of eggs laid, further contributing to reductions in transmission (Brady 2016).

Therefore, topical repellents could reduce malaria transmission by reducing an individual's probability of being bitten, while inhibiting feeding, and therefore, reducing egg production in female 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 a loss of effectiveness at a community 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 when 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 accounts for around 68% of the 660 million cases averted between 2000 and 2015 (Bhatt 2015). However, the recent stagnation in progress highlights the need for improved or new complementary interventions, or both, which address the gap that nets fail to cover. This is particularly true in settings in which 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 programmes has been linked to changes in mosquito behaviour that could limit the efficacy of intra-domiciliary interventions (Ferreira 2017; Russell 2011). Similarly, secondary vectors, such as *Anopheles arabiensis*, have replaced other species more readily targeted by these interventions (Killeen 2017).

Outdoor transmission is essential in maintaining malaria among high-risk groups living in forested areas (Carnevale 2021), including forest workers, miners, and military personnel, which in turn represents a major obstacle in malaria elimination in places like India (Ranjha 2021), the Greater Mekong Subregion (Jongdeepsais 2022), and the Amazon basin (Fletcher 2022; Saavedra 2019). Refugees are another particularly vulnerable group, given their exposure to outdoor transmission and additional risk factors, which include limited access to health services, poor sanitation and housing, and inconsistent access to vector control interventions (Semakula 2023). These factors also increase the risk of developing severe malaria in this group. Malaria represented the second most common morbidity among refugees in 2021 (18.7%), and the second most common cause of mortality in this group in 2019 (8.3% of total reported deaths (UNHCR 2022)).

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. This can also be framed within the United Nations Sustainable Development Goal 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 (long-lasting insecticide-treated nets or indoor residual spraying, or both) for reducing the incidence of malaria in high- and non-high-risk populations living in endemic areas.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized and non-randomized controlled studies in this review.

Randomized studies

We included 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 was introduced; and
- Cluster-randomized studies using a stepped-wedge approach.

Non-randomized studies

We also planned to include non-randomized studies of interventions (NRSI) that met our inclusion criteria. However, we assessed these studies separately, in a secondary analysis of observational studies for adverse effects and any summary estimates of effectiveness. We included NRSI in the search because we expected to find a limited number of randomized studies addressing the research question. We included:

- Controlled before-after studies (CBA) with baseline data, a contemporaneous control group, and at least two sites per arm, if the study had 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 assessed the methodological characteristics of each observational study design according to Cochrane Effective Practice and Organization of Care (EPOC) criteria for inclusion (EPOC 2017). For studies that met the Cochrane EPOC criteria, we used the ROBINS-I signalling questions to assess their risk of bias (Sterne 2016); if we considered the study did not present a critical risk of bias, we included it and extracted the methodological characteristics.

Types of participants

Eligible participants were children and adults who lived in a malaria-endemic area, categorized into high-risk or non-high-risk populations. For the purpose of this review, we considered high-risk populations to be populations who either did not have access to, or were less likely to benefit from programmatic vector control interventions (long-lasting insecticide-treated nets (LLINs) or indoor residual spraying (IRS)). Examples of these groups included, but were not limited to, refugees, miners, forest-goers, soldiers, or indigenous groups.

Types of interventions

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

Intervention

The interventions of interest were topical repellents, including N,N-diethyl-m-toluamide (DEET), icaridin (picaridin), 3-(N-butyl-N-acetyl)-aminopropionic acid ethyl ester (IR3535), para-menthane-3,8- diol (PMD), oil of lemon eucalyptus (OLE), N, N-diethylbenzamide, or 2-undecanone (methyl nonyl keton).

Control

Individuals in eligible control groups received a placebo or no treatment.

We excluded the data of participants infected with *P vivax* or *P ovale* from trials carried out in endemic areas for these parasites if the participants were not screened and cleared of parasites at the beginning of the trial. This was to prevent the inclusion of recrudescence cases in the analysis, since these cannot be prevented by topical repellents. Participants who received radical cure with an 8-aminoquinoline (such as primaquine), and a schizonticidal drug (such as chloroquine), were considered to be clear of latent infection, following World Health Organization (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 rapid diagnostic tests (RDTs)
- Malaria infection incidence: new *Plasmodium* spp. infections, confirmed through thick or thin blood smears, RDTs, or polymerase chain reaction (PCR)
- Malaria case and infection incidence: new *Plasmodium* spp. infection, or case of clinical malaria, confirmed through blood smears, RDTs, or 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)

Topical repellents for malaria prevention (Review)

- 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 tried to identify all relevant trials, regardless of language or publication status. We cross-referenced this list with studies included in a previous Cochrane Review that evaluated the effect of insect repellents (including topical repellents) on malaria transmission ([Maia 2018](#)), to guarantee that we included all relevant studies from that review in this one.

Electronic searches

We searched the following databases, using the search terms and strategy described in [Appendix 1](#):

- Cochrane Infectious Diseases Group Specialized Register (searched 11 January 2023, through Cochrane CENTRAL);
- Central Register of Controlled Trials (CENTRAL; 2023, issue 1), in the Cochrane Library (searched 11 January 2023);
- MEDLINE Ovid (1946 to 11 January 2023);
- Embase Ovid (1947 to 11 January 2023);
- LILACS (Latin American and Caribbean Health Science Information database; 1982 to 11 January 2023);
- CAB Abstracts (Web of Science; 1910 to 11 January 2023);
- The French Institute of Research for Development's Horizon Pleins Textes database (www.documentation.ird.fr/; searched 11 January 2023).

We also searched the WHO International Clinical Trials Registry Platform (apps.who.int/trialsearch/) and Clinicaltrials.gov (www.clinicaltrials.gov) on 11 January 2023.

Searching other resources

Conference proceedings

We searched the following conference proceedings for relevant abstracts from 2017 to 2022:

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

Organizations and pharmaceutical companies

We contacted several organizations for ongoing and unpublished trials: the WHO, Centres for Disease Control and Prevention, United States Agency for International Development, Deployed War Fighter Protection Program, London School of Hygiene and Tropical Medicine, and the Liverpool School of Tropical Medicine.

Reference lists

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

Data collection and analysis

Selection of studies

Two review authors (MGW and JCGF) independently assessed the titles and abstracts of trials identified by the searches. Four review authors (MGW, CW, LBA, and JCGF) independently assessed full-text copies of potentially relevant trials for inclusion, using an eligibility form based on the inclusion criteria. We compared included trials, and resolved disagreements by discussion and consensus, with arbitration by the fifth review author (MFM). We ensured that multiple publications of the same trial were only included once. Despite reporting the same trial, we included [Gryseels 2015](#) and [Sluydts 2016](#) separately, since they measured one secondary outcome of this review differently (adherence to intervention). We listed excluded studies, with their reasons for exclusion, in the [Characteristics of excluded studies](#) table.

Data extraction and management

Four review authors (MGW, CW, LBA, and JCGF) independently extracted information from the trials using pre-piloted, electronic data extraction forms. In case of differences in extracted data, the four review authors discussed these differences to reach consensus. If unresolved, further discussion involved the fifth author (MFM). In case of missing data, we contacted the original trial author(s) for clarification.

For all eligible studies, we extracted data on the following.

- 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
- Participants: trial settings, population characteristics, whether participants were considered a high-risk population, and if so, in which category they would fit (for example: displaced populations, such as refugees, forest goers, or deployed military); whether participants were 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
- Intervention: description of intervention; co-interventions; description of controls
- Outcomes: definition of outcome; number of participants; power; unit of analysis; incomplete outcomes/missing data; time of follow-up; passive or active case detection; compliance

For dichotomous outcomes, we extracted the number of participants experiencing each outcome and the number of participants in each treatment group, cluster-adjusted risk, or odd ratios (OR), and standard errors (SE). For count data outcomes, we extracted the number of events 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

continuous outcomes (time to first infection in months), we extracted the mean and a measure of variance, if available (range).

RCTs randomized by the individual

We extracted information on the number of participants randomized to each treatment arm, and the number of events in each of the treatment arms.

cRCTs

For cRCTs we recorded the number of clusters randomized; number of clusters analysed; measure of effect (such as rate ratio, risk ratio (RR), odds ratio (OR), or mean difference (MD)) with confidence intervals (CI) or standard deviations; number of participants; and the intra-cluster correlation coefficient (ICC) value.

Other studies

For NRSI that we considered eligible for inclusion according to [EPOC 2017](#) criteria, and not considered to be at critical risk of bias ([Sterne 2016](#)), we extracted data on estimates of effectiveness and adverse events.

Assessment of risk of bias in included studies

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

Randomized studies

Two review authors (MGW and JCGF) independently assessed the risk of bias of each study using the Cochrane RoB 2 ([Higgins 2022a](#); [Sterne 2019](#)).

We assessed the risk of bias across the different studies that measured our primary outcomes, and the incidence of adverse events.

The two review authors (MGW and JCGF) resolved any discrepancies through discussion or by consulting a third review author (MFM). We assessed the risk of bias according to the following domains ([Higgins 2022b](#)):

- Bias arising from the randomization process;
- Bias due to deviations from intended interventions;
- Bias due to missing outcome data;
- Bias in measurement of the outcome; and
- Bias in the selection of the reported result.

For cluster-randomized clinical trials, we added 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 2022c](#)).

We used the Cochrane ROB 2 tool to evaluate and determine the risk of bias of each domain across the different studies. The overall judgement of risk of bias depended on the classification of each individual domain. We classified studies in which we determined the risk of bias of at least one domain to be high, or presented some concerns, as presenting that same risk of bias.

We used the risk of bias Excel tool (available from www.riskofbias.info/), and made a summary of the risk of bias by each outcome within and across studies ([Higgins 2022b](#)).

Non-randomized studies

For NRSI, two review authors (MGW and JCGF) independently assessed the risk of bias using the ROBINS-I tool ([Sterne 2016](#)). For each outcome, we answered signalling questions to systematically judge the risk of bias and provide the basis for an overall risk of bias judgement. The signalling questions assessed bias according to seven different domains.

- Bias due to confounding
- Bias in selection of participants into the study
- Bias in classification of interventions
- Bias due to deviations from intended interventions
- Bias due to missing data
- Bias in measurement of outcomes
- 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 post-intervention.

We judged the risk of bias to be low, moderate, serious, or critical. If any domain reached critical risk of bias, we stopped the assessment and excluded the study.

For the evaluation of bias due to confounding, we also assessed the following subdomains.

- 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 therefore, can be a predictor of malaria risk.

In the review, we presented the risk of bias assessments for RCTs and NRSI using outcome-level traffic light plots created using [RevMan Web 2023](#).

Measures of treatment effect

We compared intervention and control data using incidence rate ratios (IRR) for count data, or OR for dichotomous outcomes, and presented them with their associated 95% CIs.

Unit of analysis issues

We combined results from cRCTs with individual RCTs, accounting for cluster adjustment. For count data, we extracted cluster-adjusted IRRs directly from the studies and included them in the meta-analysis, using the general inverse variance method ([Higgins 2022c](#)).

For dichotomous data, we extracted the cluster-adjusted ORs reported by individual studies and included them in the meta-analysis, as described above. For studies in which adjusted ORs were not reported, we extracted the number of participants and events in both treatment arms and adjusted for the cluster effect using existing methods, and based on the reported ICC ([Higgins 2022c](#)). If the trial did not report the ICC value, we used one from a similar, methodologically-sound study. If cluster adjustment was not possible, we excluded the cRCT from the meta-analysis and presented its results narratively, or in a separate table. We presented results using forest plots.

Topical repellents for malaria prevention (Review)

Dealing with missing data

In cases of missing data, we only included data on the known results. For outcomes with no missing data, we carried out an intention-to-treat analysis by analysing all recruited participants in the group to which they were randomized.

Assessment of heterogeneity

We inspected forest plots for overlapping CIs and assessed statistical heterogeneity in each meta-analysis using I^2 and Chi^2 statistics. We classified heterogeneity as moderate if I^2 values were between 30% and 60%; substantial if they were between 61% and 75%; and considerable if they were between 76% and 100%. We interpreted a Chi^2 test statistic with $P \leq 0.10$ as indicative of statistically significant heterogeneity. We explored clinical and methodological heterogeneity accounting for the trial population, methods, and interventions.

Assessment of reporting biases

We did not assess reporting bias in this review, as the number of studies included in the meta-analysis (6 trials) was too low to adequately do so (Harbord 2006).

Data synthesis

We analysed data using RevMan Web 2023 software. We used a fixed-effect, or a random-effects model to calculate pooled measurements, based on the clinical and methodological heterogeneity observed in the meta-analysis. We presented data on estimates of effectiveness and adverse events from eligible NRSI, narratively.

Subgroup analysis and investigation of heterogeneity

We grouped trials and analysed them by the method used to measure incidence (whether passively detected cases of clinical malaria, or actively detected infection with *Plasmodium sp.*). We undertook other subgroup analyses aggregating studies based on whether they included background interventions (LLINS or IRS), and high-risk populations, and whether participants were randomized at the cluster or individual level. For the malaria prevalence outcome, we further disaggregated studies based on whether they were carried out in refugee camps.

Sensitivity analysis

For the primary outcomes, we performed the following sensitivity analyses:

- Exclusion of trials at high risk of bias;
- Exclusion of cRCTs;
- Exclusion of trials that were not placebo-controlled;

- For cRCTs with an estimated ICC, the impact of varying the ICC; and
- 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 assessed the certainty of the evidence for each primary outcome and the malaria prevalence outcome using the GRADE approach (Guyatt 2011), as described in Balshem 2011.

- High: we are very confident that the true effect lies close to that of the estimate of the effect
- Moderate: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect
- Low: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect
- Very low: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

Evidence from RCTs start as high certainty, but can be downgraded, provided valid reasons exist within the following five categories: risk of bias, imprecision, inconsistency, indirectness, and publication bias (Balshem 2011). Evidence from NRSI assessed with the ROBINS-I tool also starts as high-certainty evidence, but is automatically downgraded by two levels due to the inherent risk of lacking randomization. Evidence from NRSI, and rarely RCTs, 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

We summarized our findings in a summary of findings table.

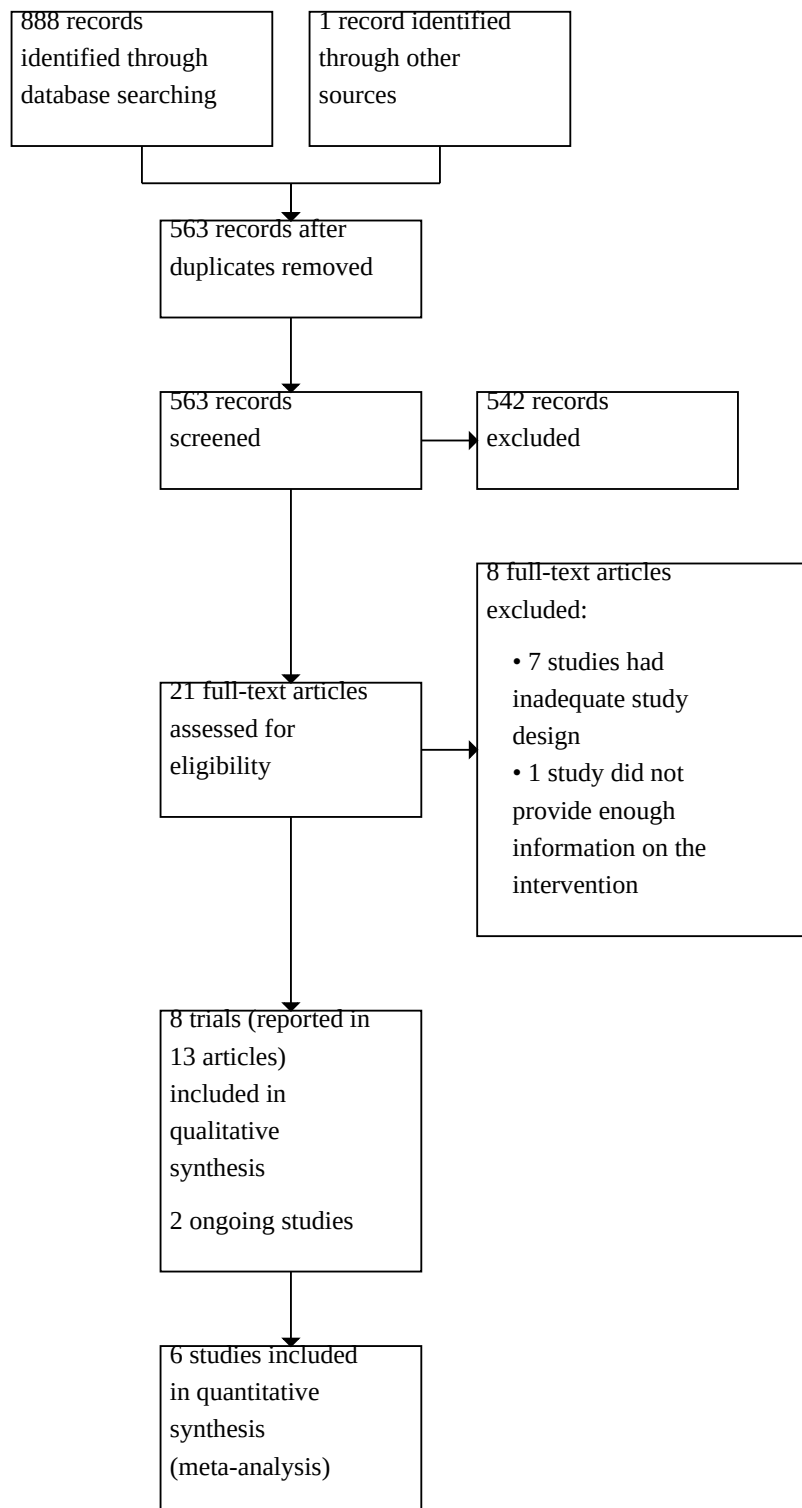
RESULTS

Description of studies

Results of the search

We searched the existing literature to 11 January 2023. We identified 888 records through electronic datasets, and one additional article was directly provided by its authors (Figure 1). After removing 326 duplicates, we performed title and abstract screening on 563 studies. Twenty-one records underwent full-text screening, of which we excluded eight. The remaining 13 records related to eight different trials, which we included in the qualitative synthesis; we included six trials in the meta-analysis.

Figure 1. PRISMA study selection flow diagram



Included studies

One randomized controlled trial (RCT (McGready 2001)), and seven cluster-RCTs (cRCTs) met the inclusion criteria of the review (Agius 2020; Chen-Hussey 2013; Hill 2007; Kroeger 1997; Rowland 2004; Sangoro 2014a; Sluydts 2016). Sluydts 2016 and Gryseels 2015 reported on the same study, but both described and analysed the outcome, adherence to treatment, differently; therefore, we presented the results independently in the qualitative synthesis. Sluydts 2016 outcomes were reported in three other publications; Agius 2020 outcomes were reported in one other publication. One of the studies was provided directly by its author, who also provided data on the number of individual participants diagnosed with malaria in each study arm, which was not reported in the published paper (McGready 2001).

For measurement of all primary outcomes (malaria infection incidence, malaria clinical case incidence, and malaria infection and case incidence together), and the secondary outcome of all-cause fever, we directly extracted cluster-adjusted incidence rate ratios (IRRs) from the published papers, and pooled them. We used a similar approach for the secondary outcome, malaria prevalence, for which we extracted reported cluster-adjusted odd ratios (ORs), and included them in the meta-analysis, using the generalized inverse variance method. For the remaining secondary outcomes, we either included the reported prevalence in the intervention and control groups to calculate odds ratios (ORs; anaemia), or included the reported results in the qualitative synthesis and corresponding tables (adverse events and adherence to treatment).

None of the studies that took place in areas where *P vivax* was endemic cleared the presence of hypnozoites prior to starting. Therefore, we excluded these studies, and only included data from *P falciparum* infections in the meta-analysis. Five studies were carried out in South or Southeast Asia (Agius 2020 in Myanmar; Chen-Hussey 2013 in Laos PDR; McGready 2001 in Thailand; Rowland 2004 in Pakistan; and Sluydts 2016 in Cambodia), two in South America (Hill 2007 in Bolivia; Kroeger 1997 in Peru and Ecuador), and one in Africa (Sangoro 2014a in Tanzania). Five studies included high-risk populations (Agius 2020; Chen-Hussey 2013; McGready 2001; Rowland 2004; Sluydts 2016), two of which were carried out in refugee camps (McGready 2001; Rowland 2004). All studies included adults and children, except McGready 2001, which only included pregnant women. In total, 61,651 participants (31,488 in the intervention arm and 30,163 in the controls) and approximately 54,657 person-years (27,967 in the intervention arm, and 26,690 in the control group) were included in the assessment of the malaria infection and clinical case incidence outcome. We included 55,366 participants (25,429 in the intervention arm, and 29,937 in controls) in the assessment of the effect on malaria prevalence.

The type and concentration of the interventions used varied, and included: 12% N-diethylbenzamide (Agius 2020), 15% DEET (Chen-Hussey 2013), 30% PMD (Hill 2007), 0.5% DEET + 20% permethrin (Kroeger 1997), 20% DEET (McGready 2001), 20% DEET + 0.5% permethrin (Rowland 2004), 15% DEET (Sangoro 2014a), and 10% or 20% picaridin (Sluydts 2016).

Excluded studies

We excluded eight studies upon full-text screening. We excluded seven due to inadequate study design (Constantini 2004; Dadzie 2013; Lindsay 1998; Maia 2012; Moore 2007; Rowland 2004b; Uzzan

2009), and one for not providing enough information on the applied intervention (Deressa 2014). We listed the detailed reasons for excluding these individual studies in the [Characteristics of excluded studies](#) table.

Ongoing studies

We identified two ongoing studies whose results have not been yet published (NCT02938975; NCT05117567).

Risk of bias in included studies

We assessed the risk of bias for our primary outcomes (malaria case and infection incidence) in four studies (clinical case incidence in Sluydts 2016; infection incidence in Chen-Hussey 2013, Hill 2007, and McGready 2001). Similarly, despite being secondary outcomes, we assessed the risk of bias for adverse events in seven studies (Agius 2020; Chen-Hussey 2013; Hill 2007; Kroeger 1997; McGready 2001; Rowland 2004; Sluydts 2016); and for the malaria prevalence outcome in four studies (Agius 2020; McGready 2001; Rowland 2004; Sluydts 2016).

Malaria case and infection incidence

Only one study included for the assessment was classified as having a low risk of bias (Chen-Hussey 2013). Two studies were classified as having a high risk of bias (Hill 2007; McGready 2001), and one as having some concerns (Sluydts 2016). The reasons for this were mostly related to issues in the randomization process, the distribution or concealment of placebos, or the presence of unexplained losses to follow-up.

Adverse events

Four studies were classified as presenting some concerns (Agius 2020; Chen-Hussey 2013; Rowland 2004; Sluydts 2016), and three presented a high risk of bias (Hill 2007; Kroeger 1997; McGready 2001). The reasons for this were mostly related to issues in the definition of adverse events, and the lack of description of the methods used to measure and report their incidence, as well as issues in the randomization process.

Malaria prevalence

Three studies were classified as having some concerns (Agius 2020; Rowland 2004; Sluydts 2016), and one was classified at high risk of bias (McGready 2001). In general, most studies presented issues with the randomization process, as well as the distribution and concealment of placebos among participants in the control groups.

A complete risk of bias assessment can be found on [Analysis 1.1](#) and [Analysis 1.5](#).

Effects of interventions

See: [Summary of findings 1 Topical repellents versus placebo or no treatment in adults and children living in malaria-endemic areas](#)

Primary outcomes

Malaria case incidence

Only one study measured clinical case incidence (Sluydts 2016), and failed to find an effect following the use of topical repellents (IRR 0.66, 95% CI 0.32 to 1.36; 1 study, 48,838 participants; low-certainty evidence; [Analysis 1.1](#)). While Sangoro 2014a also reported data on this outcome, we were unable to extract a cluster-

adjusted IRR; thus we excluded this study from the meta-analysis. This study failed to demonstrate an effect of topical repellents on malaria incidence (68.29 malaria cases per 1000 people (95% CI 37.05 to 99.53) in the control group, and 60.45 cases per 1000 people (95% CI 48.30 to 72.60) in the intervention group). [Kroeger 1997](#) also reported malaria case incidence, but the outcome was not confirmed via microscopy, rapid diagnostic tests (RDTs), or polymerase chain reaction (PCR), so we excluded it from the meta-analysis.

Malaria infection incidence

Three studies investigated the effect of topical repellents on malaria infection incidence, regardless of the development of symptomatology ([Chen-Hussey 2013](#); [Hill 2007](#); [McGready 2001](#)). Topical repellents failed to reduce infection incidence (IRR 0.76, 95% CI 0.56 to 1.02; 12,813 participants, low-certainty evidence; [Analysis 1.1](#)).

However, when we pooled data from these two subgroups, we observed a reduction of malaria incidence in the topical repellent groups (IRR 0.74, 95% CI 0.56 to 0.98; 4 studies, 61,651 participants, low-certainty evidence; [Analysis 1.1](#)).

Subgroup analysis

We carried out further subgroup analysis, disaggregating studies by whether other background vector control interventions (LLINS or IRS, or both) were used; and by whether they included high-risk groups. The only study in which nets were not provided as a background intervention was [McGready 2001](#). Eliminating this study from the meta-analysis translated into the lack of effect of repellents on malaria incidence (IRR 0.78, 95% CI 0.51 to 1.18; 3 studies, 60,754 participants; [Analysis 1.2](#)).

In the three studies that included at least one group of individuals classified as high-risk, repellents failed to cause a reduction in malaria incidence (IRR 0.76, 95% CI 0.58 to 1.01; 3 studies, 57,643 participants; [Analysis 1.3](#)). Only [Hill 2007](#) did not explicitly indicate the inclusion of any participants belonging to high-risk groups, and also failed to see a reduction in malaria (IRR 0.18, 95% CI 0.02 to 1.4; 1 study, 4008 participants).

Sensitivity analysis

We performed a series of sensitivity analyses to evaluate the effect of excluding studies with a high risk of bias, cRCTs, and studies that did not include a placebo in the control group, from the meta-analysis.

When we excluded studies with a high risk of bias ([Hill 2007](#); [McGready 2001](#)), we observed no reduction in malaria case and infection incidence (IRR 0.83, 95% CI 0.54 to 1.27; 56,746 participants).

We observed similar results after excluding cRCTs and leaving only [McGready 2001](#) (IRR 0.71, 95% CI 0.49 to 1.04; 897 participants); and those without placebo control (excluding [Sluydts 2016](#), IRR 0.76, 95% CI 0.56 to 1.02; 12,813 participants).

We intended to study the effect of adherence on the effect of repellents, by carrying out a meta-analysis with data from reported per-protocol analysis (PPA). While [Chen-Hussey 2013](#) and [Hill 2007](#) reported a PPA, a sensitivity analysis including only PPA data was not possible, since neither cluster-adjusted IRRs nor the number

of cases were aggregated by the different levels of compliance in [Chen-Hussey 2013](#). [Hill 2007](#) exclusively provided PPA data, but this was treated as an ITT analysis and included in the overall meta-analysis, given the low number of participants excluded (1.5% in both groups).

Secondary outcomes

Adverse events

Seven studies reported adverse events ([Agius 2020](#) used 12% N, N-diethylbenzamide, [Chen-Hussey 2013](#): 15% DEET, [Hill 2007](#): PMD: 30% + eucalyptus extract, [Kroeger 1997](#): 0.5% DEET and 20% permethrin, [McGready 2001](#): 20% DEET, [Rowland 2004](#): 20% DEET + 0.5% permethrin and [Sluydts 2016](#) used picaridin).

Only [Chen-Hussey 2013](#) reported the incidence of adverse events in both study arms, while the remaining studies either reported no adverse events, or just indicated those that occurred in the intervention arm.

In three studies, adverse events were passively reported by participants to community health workers or study volunteers ([Agius 2020](#); [Rowland 2004](#); [Sluydts 2016](#)). In two studies, participants were actively asked about the occurrence of adverse events during each study visit ([Chen-Hussey 2013](#); [Hill 2007](#)). [McGready 2001](#) did not provide information about how adverse events were reported. [Kroeger 1997](#) reported adverse events associated with the intervention, but later indicated that a large proportion were apparently caused by ectoparasite infestations.

In general, the prevalence of adverse events was very low, with 283 adverse events reported among 47,515 participants who received interventions (0.6%, [Table 1](#)[Analysis 1.4](#)), and limited to mild skin reactions. The prevalence of adverse reactions in all studies remained below 0.1%, except for [McGready 2001](#) (11.4%), which included only pregnant women; [Kroeger 1997](#) (3%), and [Chen-Hussey 2013](#), in which prevalence was also higher in the intervention group (3.8% in the intervention arm and 3.2% in controls, $P = 0.029$).

Malaria prevalence

Four studies evaluated the effect of topical repellents on malaria prevalence ([Agius 2020](#); [McGready 2001](#); [Rowland 2004](#); [Sluydts 2016](#)). For [Sluydts 2016](#), four independent surveys, using PCR to diagnose infection, were carried out between 2012 and 2013. These surveys were individually included in the meta-analysis. For all the cRCTs ([Agius 2020](#); [Rowland 2004](#)); and the four individual surveys in [Sluydts 2016](#), we used the cluster-adjusted OR reported by the study authors.

In general, repellents caused a 19% reduction in malaria prevalence (OR 0.81, 95% CI 0.67 to 0.97; 4 studies, 55,366 participants; low-certainty evidence; [Analysis 1.5](#)). While all studies included at least some participants belonging to a high-risk group, a subgroup analysis revealed that the effect was mostly driven by two studies carried out in refugee camps ([McGready 2001](#); [Rowland 2004](#)), in which all participants were classified as high-risk (OR 0.61, 95% CI 0.44 to 0.86; 2045 participants). These were also the only studies in which nets were not used as a background intervention. This effect was not observed if these studies were excluded from the meta-analysis (OR 0.90, 95% CI 0.73 to 1.11; 2 studies, 53,321 participants).

Topical repellents for malaria prevention (Review)

Differences between both groups were maintained upon exclusion of studies that were not placebo-controlled (the four surveys from [Sluydts 2016](#) (OR 0.73, 95% CI 0.58 to 0.91; 34,239 participants)), but not after excluding those with a high risk of bias ([McGready 2001](#); OR 0.82, 95% CI 0.67 to 1.00; 54,469 participants).

Only [Agius 2020](#) and [Sluydts 2016](#) reported PPA data, with [Agius 2020](#) further dividing participants based on whether they used the repellent on a monthly, weekly, or daily basis. For the PPA sensitivity analysis, reported ORs from [Agius 2020](#) were pooled with the reported PPA OR from [Sluydts 2016](#). This evidenced no effect on malaria prevalence (OR 0.81, 95% CI 0.42 to 1.56; 32,824 participants; [Analysis 1.6](#)), regardless of whether the data from participants who used the repellent on a monthly (OR 0.86, 95% CI 0.44 to 1.69), weekly (OR 0.80, 95% CI 0.40 to 1.60), or daily basis (OR 0.78, 95% CI 0.39 to 1.57) were incorporated into the meta-analysis.

Anaemia

One included study investigated the impact on anaemia ([McGready 2001](#)). Topical repellents had no impact on this outcome (OR 1.12, 95% CI 0.81 to 1.55; 1 study, 587 participants; [Analysis 1.7](#)).

Time to first infection

One included study reported this outcome ([Chen-Hussey 2013](#)). They found no effect of topical repellents (intervention group: mean time to first infection: 4 months, range 0.9 to 7.5 months; control group: 3.9 months, range 0.7 to 7.5 months).

All-cause fever

One study investigated the impact on all-cause fever ([Hill 2007](#)). Participants who used topical repellents were less than half as likely to develop a fever when compared to participant in the control arm (IRR 0.42, 95% CI 0.32 to 0.56; 1 study, 4008 participants; [Analysis 1.8](#)).

Incidence of severe malaria

No results were found for this outcome.

Malaria-related mortality

No results were found for this outcome.

Adherence to the regular usage of the intervention

All included studies measured the adherence to the intervention ([Table 2](#); [Analysis 1.9](#)). However, the way this was measured varied substantially and results were diverse.

In three studies, adherence was exclusively self-reported by participants ([Kroeger 1997](#); [Rowland 2004](#); [Sluydts 2016](#)). In another three studies, it was exclusively reported through observations by study workers during field visits ([Agius 2020](#); [Hill 2007](#); [Sangoro 2014](#)). In another three studies, authors reported both self-reported, and observed adherence ([Chen-Hussey 2013](#); [Gryseels 2015](#); [McGready 2001](#)). The methods used to measure observed adherence were: estimating the weight of returned repellent bottles ([Chen-Hussey 2013](#); [Hill 2007](#)), random sniff checks to smell the arms of participants to determine if the repellent had been applied ([Chen-Hussey 2013](#); [Gryseels 2015](#); [Hill 2007](#); [McGready 2001](#)), or counting the number of bottles issued to individual households ([Sangoro 2014](#)).

Four studies reported a very high adherence in the intervention group: [Hill 2007](#) (98.5%), [Kroeger 1997](#) (81.9% in Ecuador and 91.3% in Peru), [McGready 2001](#) (90.5%), and [Rowland 2004](#) (95%). Adherence was not directly reported by [Sangoro 2014a](#), but was estimated to be of approximately 99.2%, based on differences between the samples used in the ITT and PPA analyses. There was a difference between self-reported and observed adherence in [Chen-Hussey 2013](#) (self-reported 61.3%, observed 47.4%); [Gryseels 2015](#) (self-reported 34%, observed 7.9%); and [McGready 2001](#) (self-reported 90.5%, observed 84.6%).

The adherence reported by [Sluydts 2016](#) (72% and 69% in two successive self-reported surveys) was also different from that reported by [Gryseels 2015](#) (self-reported 34%, observed 7.9%), even though both papers refer to the same clinical trial. These differences are likely explained by the way the question was asked in the two questionnaires; [Sluydts 2016](#) asked if participants had used the repellent the day before, and [Gryseels 2015](#) asked about the continuous use of the lotion throughout the entire study period.

Human biting rate

This was only reported by [Kroeger 1997](#), as 9.5 bites per hour in participants who received the intervention and remained resting, and 15.4 in those who exercised; compared to 40 bites per hour in controls ($P < 0.01$).

Entomological inoculation rate

No results were found for this outcome.

Sporozoite rate

No results were found for this outcome.

Human blood index

No results were found for this outcome.

DISCUSSION

Summary of main results

See [Summary of findings 1](#).

Our results suggest that the effect of topical repellents on malaria incidence and prevalence is being driven by reductions in participants from high-risk groups without access to other vector control interventions. These results are based on five cluster-randomized controlled trials (cRCTs) and one RCT. None of the studies included in this review cleared the presence of hypnozoites before starting. Therefore, the meta-analysis only accounted for cases and infections caused by *P. falciparum*.

The effect of topical repellents on malaria incidence

Topical repellents may make little or no difference to the incidence of clinical malaria and infection with *P. falciparum* when these outcomes are evaluated separately. However, these results were based on only two cRCTs and one RCT measuring infection incidence, and one cRCT measuring clinical case incidence. When data from all these studies were pooled and treated as a single malaria incidence outcome, we observed a slight reduction in malaria incidence (6 fewer events per 1000 person-years in the intervention arm, incidence rate ratios (IRR) 0.74, 95% confidence

interval (CI) 0.56 to 0.98), but the certainty of evidence for this outcome was low.

We observed no effect of the intervention when we disaggregated studies based on the use of other background interventions, although the only study in which these were not used contributed to 56% of the overall weight of the meta-analysis (McGready 2001).

A subgroup analysis, grouping studies by whether they included participants who belonged to high-risk groups, failed to show an effect on either group. It is important to note that Hill 2007 was the only study we considered did not include high-risk populations, since these were not explicitly described by the authors. Nonetheless, it is possible that some of the participants included in the study participated in high-risk activities, given the location of the studied communities near forest areas.

The effect of topical repellents on malaria prevalence

Topical repellents may also slightly reduce *P falciparum* prevalence, with two fewer events per 1000 participants in the intervention arm (odds ratio (OR) 0.81, 95% CI 0.67 to 0.97). However, the certainty of evidence for this outcome was also low.

A subgroup analysis revealed that this effect was mostly driven by two studies carried out in refugee camps (OR 0.61, 95% CI 0.44 to 0.86), which accounted for 27.7% of the weight in the meta-analysis, and in which no long-lasting insecticide treated nets (LLINs) were being used at the time (McGready 2001; Rowland 2004).

We are unable to determine if this beneficial effect would still be observed with the concurrent use of LLINs, which currently represents a standard malaria vector control intervention.

Adverse events associated with topical repellents

Adverse events associated with the use of topical repellents were rare, with an overall prevalence of 0.6% among 47,515 participants receiving interventions. In all these cases, adverse events were limited to mild skin reactions. Three studies reported a prevalence of adverse events above 1%. Participants from McGready 2001 were pregnant women living in a refugee camp, and might have been exposed to certain confounding factors that explained their higher prevalence of adverse events. Similarly, an unspecified proportion of skin reactions described by Kroeger 1997 were attributed to ectoparasite infestation. Data on adverse events were not included in the meta-analysis, since only Chen-Hussey 2013 reported adverse events in both intervention arms. Results from this study suggest that these were linked to the use of repellents (prevalence of 3.8% in the intervention arm and 3.2% in controls, $P = 0.029$).

The effect of adherence to the use of topical repellents

The influence of adherence to the intervention on the effect of topical repellents on malaria incidence could not be demonstrated in this review, as data from most studies that reported a (per-protocol analysis) PPA could not be included in the meta-analysis. Nonetheless, PPA results reported by Agius 2020 and Sluydts 2016 indicated that the regular use of repellents did not lead to a reduction of malaria prevalence in those studies.

The methods used to measure adherence varied across studies, and might not reflect the real compliance of participants. Measuring the adherence to the correct use of topical repellents is complex and

logistically difficult, considering the lack of a standardized method to do so, and the varying degrees to which a participant can comply with instructions provided by study workers. This is demonstrated by the diverse estimates derived from different inter- and even intra-study analysis.

In general, adherence observed by study workers was lower than that self-reported by participants. A particularly large difference between these two outcomes was reported in Gryseels 2015 (self-reported adherence of 34% versus observed adherence of 7.9%), suggesting that self-reported adherence is likely inflated due to respondent bias. This publication also thoroughly described the methods used to measure observed adherence, which included unannounced visits to randomly selected houses to perform sniff checks and observe the correct application of the repellent. These are likely to provide the most objective ascertainment of the real level of adherence in a cohort.

The effect of topical repellents on other outcomes

An effect of topical repellents was not observed for anaemia (McGready 2001), or the time to first malaria infection (Chen-Hussey 2013). However, each one of these outcomes was reported by a single study. A 58% reduction in all-cause fever was reported by Hill 2007. Reductions in the human biting rate of mosquitoes were reported by Kroeger 1997, and associated with the use of topical repellents. None of the included studies reported data for the effect of the intervention on the entomological inoculation rate, the sporozoite rate, or the human blood index of mosquitoes.

Overall completeness and applicability of evidence

Most studies included participants from all age groups. However, as previously noted, one study only included pregnant women living in a refugee camp (McGready 2001). Given the significant contribution of this study to the results of our meta-analysis, it is possible that our findings are not generalizable to other groups.

The results from studies that included participants in high-risk groups accounted for 98.2% of the weight in the meta-analysis of malaria incidence.

Similarly, all the studies that evaluated the effects on malaria prevalence included participants belonging to at least one high-risk group. The two studies carried out in refugee camps contributed to 28% of the weight of the effect on this outcome, despite having a disproportionately smaller population than the rest (McGready 2001; Rowland 2004). These results suggest that the observed reduction in malaria transmission is likely more important among these high-risk groups, and not generalizable to the rest of the population.

Studies included in the meta-analyses were carried out in diverse geographical settings, including Bolivia (Hill 2007), Cambodia (Sluydts 2016), Laos DPR (Chen-Hussey 2013), Myanmar (Agius 2020), Pakistan (Rowland 2004), and Thailand (McGready 2001). Only Sangoro 2014a was carried out in Africa (Tanzania), but we did not include its results in the meta-analysis because we were unable to extract the necessary information on cluster-adjusted estimates of effect.

The baseline malaria incidence (calculated from the number of cases/100 person-years in the control arm) of most studies was low (39.8 cases per 100 person-years in McGready 2001; 2.18 in Sluydts 2016; 1.5 in Chen-Hussey 2013; and 0.96 in Hill 2007). Furthermore,

Topical repellents for malaria prevention (Review)

these incidence rates were lower than those used to estimate corresponding sample sizes (5.0 in [Sluydts 2016](#); 2.0 in [Chen-Hussey 2013](#); 10.0 in [Hill 2007](#)), indicating that most of these studies were underpowered to detect changes in the outcomes of interest.

A similar situation was observed with studies reporting prevalence; most studies reported prevalences below those used to estimate their sample sizes: reported prevalence of 8.9% versus 12% used for sample size calculations ([Rowland 2004](#)), and 1.62% versus 5% ([Sluydts 2016](#)). The reported malaria prevalence in [Agius 2020](#) was 0.05% when using rapid diagnostic tests (RDTs) to measure the outcome (versus 1% used for sample size calculation), but rose to 1.74% when using polymerase chain reactions (PCRs), highlighting the advantages of this technique to measure infection outcomes in trials taking place in areas of low endemicity. [McGready 2001](#) did not report the assumed transmission estimate used to calculate the study sample size, but is less likely to be underpowered, considering the high baseline incidence (39.8 cases per 100 person-years) and prevalence (11.38%) reported by the trial authors.

The amount by which studies were underpowered was worsened by the use of large clusters, as was seen in two studies: [Agius 2020](#) (average cluster size: 2230 participants, design effect: 345.8) and [Sluydts 2016](#) (average cluster size: 498 participants, design effect: 15.62). While this was partially addressed by including the cluster-adjusted OR reported by authors in the meta-analysis, rather than using the design effect to manually adjust the reported prevalences, it illustrates the problems derived from using this experimental design in low-endemicity areas. In both studies, this was a direct consequence of randomizing entire villages, as already noticed in a previous review ([Maia 2018](#)). We believe that randomizing households could pose a feasible alternative to limit the effect of cluster adjustment on effective sample size estimations, particularly in settings of low endemicity.

Most included studies in this review were cRCTs. This design results in the effect being measured at the cluster level (community protection) rather than at the individual level (personal protection). To understand whether topical repellents provide protection at the individual level, adherence can be evaluated and considered when measuring protective effect. However, at the cluster-level, it is virtually impossible to differentiate the lack of effect derived from poor adherence, from that caused by a poor protective effect by the intervention itself. In addition, individually randomized studies with adequate measurement of observed adherence would be required to determine whether repellents do offer personal protection. Nonetheless, these studies must consider the potential diversion of mosquitoes to unprotected participants, and take measures to quantify this phenomenon in their experimental design.

Certainty of the evidence

We assessed the evidence supporting the results of the primary outcomes to be of low-certainty. We downgraded the certainty of the evidence for incidence of malaria infection by two levels due to the high risk of bias of two studies ([Hill 2007](#); [McGready 2001](#)), and the indirectness of the population of one ([McGready 2001](#) exclusively included pregnant women), which contributed to 55.6% of the weight in the meta-analysis.

We downgraded the certainty of the evidence for the incidence of malaria cases by two levels due to high risk of bias and imprecision.

The only cRCT included in this outcome failed to administer a placebo to the control group, and presented few events and CIs that crossed the point of no effect ([Sluydts 2016](#)).

We also graded the evidence for the malaria case and infection incidence outcome, which pooled data from the two previous ones, as low-certainty.

Given its relevance to the conclusions of the review, we assessed the certainty of the evidence for malaria prevalence (secondary outcome), and also classified it as low-certainty evidence. We downgraded the evidence by two levels due to the risk of bias of a study that failed to provide a placebo intervention, despite using a stepped-wedge design that allowed participants to know when the intervention was applied ([Agius 2020](#)); and the indirectness of the population of [McGready 2001](#).

Potential biases in the review process

We attempted to minimize bias in the review process by conducting a comprehensive search of published and unpublished literature, without language restrictions. Two review authors, who were not part of the author team of the included papers, independently screened abstracts, and assessed the risk of bias, and four extracted data. We resolved discrepancies by involving a fifth review author. We were unable to create funnel plots to assess reporting biases, since fewer than 10 RCTs/cRCTs met the inclusion criteria.

Agreements and disagreements with other studies or reviews

A systematic review and meta-analysis carried out by [Wilson 2014](#) suggested that topical repellents are unlikely to provide protection against malaria, but that better designed studies were necessary before reaching a conclusion. A similar work by [Maia 2018](#) concluded that there was insufficient evidence to determine if the use of topical repellents had a beneficial effect on malaria transmission, but that this intervention could have advantages in refugee camps and disaster settings. Our results agree with these, as well as with recently published data, indicating a benefit of topical repellents in refugee camps ([Messenger 2023](#)), based on a meta-analysis that also included [McGready 2001](#) and [Rowland 2004](#).

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence to conclude that topical repellents can prevent malaria in settings where other vector control interventions are in place.

Our results suggest that repellents could have a modest beneficial effect among certain groups with poor access to these interventions, particularly refugees. This result agrees with another recently published systematic review, suggesting their potential usefulness in the context of humanitarian crises ([Messenger 2023](#)). Nonetheless, reductions in malaria incidence and prevalence were marginal, and we failed to see them in settings where nets or indoor residual spraying were widely available. The real effect of the intervention might also be different from our estimate, since the certainty of evidence for all the outcomes included in this Cochrane Review was low.

Implications for research

Similar to previous reviews (Maia 2018; Wilson 2014), we conclude that more well-designed trials that evaluate the use of topical repellents could provide further insight into their real effect on reducing malaria transmission. For instance, while cluster-randomized controlled trials (cRCTs) can provide estimates of the effect of topical repellents on malaria prevention at the community-level, their implementation in areas of low transmission is challenging, given the large sample sizes required to design adequately powered studies. Studies like Rowland 2004, which used randomization at the household level, rather than larger clusters at the village/hamlet-level, could help reduce design effects, potentially contributing to more adequately powered trials. Individually-randomized studies could also be an alternative, as they are usually less resource-demanding and provide information on personal protection. However, this is likely to produce other problems, such as contamination between the trial arms and diversion of vectors to unprotected participants, which should not be overlooked.

All trials evaluating the use of topical repellents should be placebo-controlled, due to the high risk of performance bias; and include the use of long-lasting insecticide-treated nets as a background intervention. These trials should focus on groups categorized as presenting a high risk of malaria infection, according to the criteria outlined in this review. Similarly, clearance of hypnozoites prior to study start should be included in the protocols of studies measuring the effect of topical repellents on infection caused by *P vivax* and *P ovale*, which are the predominant species in many regions where this intervention might be particularly useful. If studies include participants from groups considered high-risk, the results should be disaggregated and reported with independent effect size estimations for high- and non-high risk groups.

Despite this, existing evidence indicates that topical repellents are unlikely to provide substantial protection to groups already benefiting from other malaria vector control interventions.

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Editorial and peer-reviewer contributions

The following people conducted the editorial process for this review:

- Sign-off Editor (final editorial decision): Dr Hellen Gelband, 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 and production): Victoria Pennick, Cochrane Central Production Service
- Peer-reviewers (provided comments and recommended an editorial decision):
 - Sarah J Moore, Ifakara Health Institute, Bagamoyo Tanzania; Swiss Tropical and Public Health Institute, Allschwil, Switzerland; Katherine Gleave, Liverpool School of Tropical Medicine; Tilly Fox, Liverpool School of Tropical Medicine* (content review)
 - Brian Duncan (consumer review)
 - Marty Chaplin, CIDG* (statistical review)
 - Ina Monsef, Cochrane Haematology, Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf, Faculty of Medicine and University Hospital Cologne, University of Cologne, Germany (search review).

*Tilly Fox and Marty Chaplin are CIDG members, and provided peer-review comments on this article, but were not otherwise involved in the editorial process or decision-making for this article.

REFERENCES

References to studies included in this review

Agius 2020 {published data only}[10.1371/journal.pmed.1003177](#)

* Agius PA, Cutts JC, Han Oo W, Thi A, O'Flaherty K, Zayar Aung K, et al. Evaluation of the effectiveness of topical repellent distributed by village health volunteer networks against *Plasmodium* spp. infection in Myanmar: a stepped-wedge cluster randomised trial. *PLoS Medicine* 2020;**17**(8):e1003177. [DOI: [10.1371/journal.pmed.1003177](#)]

Win Han Oo, Cutts JC, Agius PA, Kyaw Zayar Aung, Poe Poe Aung, Aung Thi, et al. Effectiveness of repellent delivered through village health volunteers on malaria incidence in villages in South-East Myanmar: a stepped-wedge cluster-randomised controlled trial protocol. *BMC Infectious Diseases* 2018;**18**:663.

Chen-Hussey 2013 {published data only}

Chen-Hussey V, Carneiro I, Keomanila H, Gray R, Bannavong S, Phanalasy S, et al. Can topical insect repellents reduce malaria? A cluster-randomised controlled trial of the insect repellent N,N-diethyl-m-toluamide (DEET) in Lao PDR. *PLoS One* 2013;**8**(8):e70664.

Gryseels 2015 {published data only}[10.1038/srep16847](#)

Gryseels C, Uk S, Sluydts V, Durnez L, Phoeuk P, Suon S, et al. Factors influencing the use of topical repellents: implications for the effectiveness of malaria elimination strategies. *Scientific Reports* 2020;**15**:16847. [DOI: [10.1038/srep16847](#)]

Hill 2007 {published data only}[10.1136/bmj.39356.574641.55](#)

Hill N, Lenglet A, Arnéz AM, Carneiro I. Plant based insect repellent and insecticide treated bed nets to protect against malaria in areas of early evening biting vectors: double blind randomised placebo controlled clinical trial in the Bolivian Amazon. *BMJ* 2007;**335**(7628):1023.

Kroeger 1997 {published data only}

Kroeger A, Gerhardus A, Kruger G, Mancheno M, Pesse K. The contribution of repellent soap to malaria control. *American Journal of Tropical Medicine and Hygiene* 1997;**56**(5):580-4. [DOI: [10.4269/ajtmh.1997.56.580](#)]

McGready 2001 {published data only}

McGready R, Simpson JA, Htway M, White NJ, Nosten F, Lindsay SW. A double-blind randomized therapeutic trial of insect repellents for the prevention of malaria in pregnancy. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2001;**95**(2):137-8. [DOI: [10.1016/S0035-9203\(01\)90137-3](#)]

Rowland 2004 {published data only}

Rowland M, Downey G, Rab A, Freeman T, Mohammad N, Rehman H, et al. DEET mosquito repellent provides personal protection against malaria: a household randomized trial in an Afghan refugee camp in Pakistan. *Tropical Medicine & International Health* 2004;**9**(3):335-42. [DOI: [10.1111/j.1365-3156.2004.01198.x](#)]

Sangoro 2014a {published data only}

Miller JE. Low cost repellents for malaria prevention in rural Africa: the jury is still out. *American Journal of Tropical Medicine and Hygiene* 2011;**6**(Suppl 1):369-70.

* Sangoro O, Turner E, Simfukwe E, Miller JE, Moore SJ. A cluster-randomized controlled trial to assess the effectiveness of using 15% DEET topical repellent with long-lasting insecticidal nets (LLINs) compared to a placebo lotion on malaria transmission. *Malaria Journal* 2014;**13**:324. [DOI: [10.1186/1475-2875-13-324](#)]

Sangoro P, Simfukwe E, Moore SJ. Cluster randomized controlled trial to determine the additional benefits of topical repellents to long lasting insecticide nets (LLINs) on malaria incidence. *American Journal of Tropical Medicine and Hygiene* 2011;**6**(Suppl. 1):229.

Sluydts 2016 {published data only}[10.1016/S1473-3099\(16\)30148-7](#)

Cooseman M. Evaluation of topical repellents as additional vector control measures to control residual transmission in malaria pre-elimination areas. 63rd Annual Meeting of the American Society of Tropical Medicine and Hygiene. 2014 November 2 - 6; New Orleans (LA). *American Journal of Tropical Medicine and Hygiene* 2014;**91**(Suppl 5):A 657.

Heng S, Sluydts V, Durnez L, Mean V, Polo K, Tho S, et al. Safety of a topical insect repellent (picaridin) during community mass use for malaria control in rural Cambodia. *PLoS One* 2017;**12**(3):e0172566.

Mao S, Durnez L, Coosemans M. The effectiveness of a topical repellents and long-lasting insecticidal nets on mosquito populations in a malaria preelimination setting of Cambodia. *Tropical Medicine & International Health* 2017;**22**:22-3.

* Sluydts V, Durnez L, Heng S, Gryseels C, Canier L, Kim S, et al. Efficacy of topical mosquito repellent (picaridin) plus long-lasting insecticidal nets versus long-lasting insecticidal nets alone for control of malaria: a cluster randomised controlled trial. *Lancet Infectious Diseases* 2016;**16**(10):1169-77.

References to studies excluded from this review

Constantini 2004 {published data only}[10.1016/j.trstmh.2003.12.015](#)

Constantini C, Badolo A, Ilboudo-Sanogo E. Field evaluation of the efficacy and persistence of insect repellents DEET, IR3535, and KBR 3023 against *Anopheles gambiae* complex and other Afrotropical vector mosquitoes. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2004;**98**(11):644-52.

Dadzie 2013 {published data only}

Dadzie S, Boakye D, Asoala V, Koram K, Kiszewski A, Appawu M. A community-wide study of malaria reduction: evaluating efficacy and user-acceptance of a low-cost repellent in northern Ghana. *American Journal of Tropical Medicine and Hygiene* 2013;**88**:309-14.

Deressa 2014 {published data only} [10.1186/1756-3305-7-132](#)

Deressa W, Yihdego YY, Kebede Z, Batisso E, Tekalegne A, Dagne GA. Effect of combining mosquito repellent and insecticide treated net on malaria prevalence in Southern Ethiopia: a cluster-randomised trial. *Parasites & Vectors* 2014;**7**:132.

Lindsay 1998 {published data only}

Lindsay SW, Ewald JA, Samung, Apiwathnasorn C, Nosten F. Thanaka (*Limonia acidissima*) and DEET (di-methyl benzamide) mixture as a mosquito repellent for use by Karen women. *Medical and Veterinary Entomology* 1998;**12**(3):295-301.

Maia 2012 {published data only}

Maia MF, Onyango SP, Thele M, Simfukwe ET, Turner EL, Moore SJ. Do topical repellents divert mosquitoes within a community? Health equity implications of topical repellents as a mosquito bite prevention tool. *PLoS One* 2013;**8**(12):e84875.

Moore 2007 {published data only}

Moore SJ, Darling ST, Sihuinchu M, Padilla N, Devine GJ. A low-cost repellent for malaria vectors in the Americas: results of two field trials in Guatemala and Peru. *Malaria Journal* 2007;**6**:101.

Rowland 2004b {published data only}

Rowland M, Freeman T, Downey G, Hadi A, Saeed M. DEET mosquito repellent sold through social marketing provides personal protection against malaria in an area of all-night mosquito biting and partial coverage of insecticide-treated nets: a case-control study of effectiveness. *Tropical Medicine & International Health* 2004;**9**(3):343-50.

Uzzan 2009 {published data only}

Uzzan B, Konate L, Diop A, Nicolas P, Dia I, Dieng Y, et al. Efficacy of four insect repellents against mosquito bites: a double-blind randomized placebo-controlled field study in Senegal. *Fundamental & Clinical Pharmacology* 2009;**23**(5):589-94.

References to ongoing studies
NCT02938975 {published data only}

Msellemu D, Ross A, Temu L, Moshi I, Hofer L, Mwanziva C, et al. Effect of interventions to reduce malaria incidence among military personnel on active duty: study protocol for a cluster randomised controlled trial of the impact of etofenprox-treated uniforms, permethrin-treated uniforms and DEET insect repellent. *Trials* 2021;**22**:825. [DOI: [10.1186/s13063-021-05801-9](#)]

NCT02938975. Field efficacy of insecticide treated uniforms and skin repellents for malaria prevention (URCT) [Field efficacy of insecticide treated uniforms and skin repellents to reduce malaria incidence in military personnel on active duty in regions of hyperendemicity]. classic.clinicaltrials.gov/ct2/show/NCT02938975 first received 19 October 2016.

NCT05117567 {published data only}

Htike W, Oo WH, Lynn T, Sovanda L, Agius PA, Oo MC, et al. Reducing malaria transmission in forest-going mobile and migrant populations in Lao PDR and Cambodia: protocol for stepped-wedge cluster-randomised controlled

trial. *BMC Infectious Diseases* 2022;**22**:747. [DOI: [10.1186/s12879-022-07724-5](#)]

NCT05117567. Reducing malaria transmission in forest-going mobile and migrant populations in Lao PDR and Cambodia [A personal protection package for reducing malaria transmission in forest-going mobile and migrant populations in Lao PDR and Cambodia: a stepped-wedge trial with nested mixed-methods study]. classic.clinicaltrials.gov/ct2/show/NCT05117567 first received 11 November 2021.

Additional references
Alpern 2016

Alpern JD, Dunlop SJ, Dolan BJ, Stauffer WM, Boulware DR. Personal protection measures against mosquitoes, ticks, and other arthropods. *Medical Clinics of North America* 2016;**100**(2):303-16. [DOI: [10.1016/j.mcna.2015.08.019](#)]

Balshem 2011

Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. *Journal of Clinical Epidemiology* 2011;**64**(4):401-6.

Bevilacqua 2015

Bevilacqua M, Rubio-Palis Y, Medina DA, Cárdenas L. Malaria control in Amerindian communities of Venezuela: strengthening ecohealth practice throughout conservation science and capability approach. *EcoHealth* 2015;**12**(2):253-66.

Bhatt 2015

Bhatt S, Weiss DJ, Cameron E, Bisanzio D, Mappin B, Dalrymple U, et al. The effect of malaria control on *Plasmodium falciparum* in Africa between 2000 and 2015. *Nature* 2015;**526**(7572):207-11.

Brady 2016

Brady OJ, Godfray HC, Tatem AJ, Gething PW, Cohen JM, McKenzie FE, et al. Vectorial capacity and vector control: reconsidering sensitivity to parameters for malaria elimination. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2016;**110**(2):107-17. [DOI: [10.1093/trstmh/trv113](#)]

Carnevale 2021

Carnevale P, Manguin S. Review of issues on residual malaria transmission. *Journal of Infectious Diseases* 2021;**223**(12 Suppl 2):S61-80. [DOI: [10.1093/infdis/jiab084](#)]

Carter 2021

Carter TE, Yared S, Getachew D, Spear J, Choi SH, Samake JN, et al. Tracking of *Anopheles stephensi* in Ethiopia using mitochondrial DNA reveals pattern of spread. *bioRxiv* 2021. [DOI: [10.1101/2021.04.07.437873](#)]

Chaumeau 2022

Chaumeau V, Kajeechiwa L, Kulabkeeree T, Sawasichai S, Haohankhunnatham W, Inta A, et al. Outdoor residual spraying for malaria vector-control in Kayin (Karen) state, Myanmar: a cluster randomized controlled trial. *PLoS One* 2022;**17**(9):e0274320. [DOI: [10.1371/journal.pone.0274320](#)]

Topical repellents for malaria prevention (Review)

Dickens 2013

Dickens JC, Bohbot JD. Mini review: mode of action of mosquito repellents. *Pesticide Biochemistry and Physiology* 2013;**106**(3):149-55.

Douine 2020

Douine M, Lambert Y, Musset L, Hiwat L, Reis Blume L, Marchesini P, et al. Malaria in gold miners in the Guianas and the Amazon: current knowledge and challenges. *Current Tropical Medicine Reports* 2020;**7**:37-47. [DOI: [10.1007/s40475-020-00202-5](https://doi.org/10.1007/s40475-020-00202-5)]

Durnez 2013

Durnez L, Mao S, Denis L, Roelants P, Sochantha T, Coosemans M. Outdoor malaria transmission in forested villages of Cambodia. *Malaria Journal* 2013;**12**:329. [DOI: [10.1186/1475-2875-12-329](https://doi.org/10.1186/1475-2875-12-329)]

EPOC 2017

Cochrane Effective Practice and Organisation of Care (EPOC). What study designs should be included in an EPOC review and what should they be called? epoc.cochrane.org/epoc-resources-review-authors (accessed 7 July 2021).

Ferreira 2017

Ferreira CP, Lyra SP, Azevedo F, Greenhalgh D, Massad E. Modelling the impact of the long-term use of insecticide-treated bed nets on Anopheles mosquito biting time. *Malaria Journal* 2017;**16**:373.

Fletcher 2022

Fletcher IK, Grillet ME, Moreno JE, Drakeley C, Hernández-Villena J, Jones KE, et al. Synergies between environmental degradation and climate variation on malaria re-emergence in southern Venezuela: a spatiotemporal modelling study. *Lancet Planetary Health* 2022;**6**(9):e739-48. [DOI: [10.1016/S2542-5196\(22\)00192-9](https://doi.org/10.1016/S2542-5196(22)00192-9)]

Garrett-Jones 1964

Garrett-Jones C. Prognosis for interruption of malaria transmission through assessment of the mosquito's vectorial capacity. *Nature* 1964;**204**:1173-5.

Govella 2013

Govella NJ, Chaki PP, Killeen GF. Entomological surveillance of behavioural resilience and resistance in residual malaria vector populations. *Malaria Journal* 2013;**12**:124. [DOI: [10.1186/1475-2875-12-124](https://doi.org/10.1186/1475-2875-12-124)]

Gryseels 2015

Gryseels C, Uk S, Sluydts V, Durnez L, Phoeuk P, Suon S, et al. Factors influencing the use of topical repellents: implications for the effectiveness of malaria elimination strategies. *Scientific Reports* 2015;**5**:16847. [DOI: [10.1038/srep16847](https://doi.org/10.1038/srep16847)]

Guyatt 2011

Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. *Journal of Clinical Epidemiology* 2011;**64**(4):380-2. [DOI: [10.1016/j.jclinepi.2010.09.011](https://doi.org/10.1016/j.jclinepi.2010.09.011)]

Harbord 2006

Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Statistics in Medicine* 2006;**25**(20):3443-57. [DOI: [10.1002/sim.2380](https://doi.org/10.1002/sim.2380)]

Herodotus 1996

Herodotus. The Histories. London (UK): Penguin, 1996.

Higgins 2022a

Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.3 (updated February 2022). Cochrane, 2022. Available from training.cochrane.org/handbook.

Higgins 2022b

Higgins JP, Savović J, Page MJ, Elbers RG, Sterne JA. Chapter 8: Assessing risk of bias in a randomized trial. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.3 (updated February 2022). Cochrane, 2022. Available from training.cochrane.org/handbook.

Higgins 2022c

Higgins JP, Eldridge S, Li T. Chapter 23: Including variants on randomized trials. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.3 (updated February 2022). Cochrane, 2022. Available from training.cochrane.org/handbook.

Jongdeepsaisai 2022

Jongdeepsaisai M, Khonputsa P, Prasert O, Maneenat S, Pongsoipetch K, Jatapai A, et al. Forest malaria and prospects for anti-malarial chemoprophylaxis among forest goers: findings from a qualitative study in Thailand. *Malaria Journal* 2022;**21**(1):47. [DOI: [10.1186/s12936-022-04070-4](https://doi.org/10.1186/s12936-022-04070-4)]

Killeen 2014

Killeen GF. Characterizing, controlling and eliminating residual malaria transmission. *Malaria Journal* 2014;**13**:330.

Killeen 2017

Killeen GF, Marshall JM, Kiware SS, South AB, Tusting LS, Chaki PP, et al. Measuring, manipulating and exploiting behaviours of adult mosquitoes to optimise malaria vector control impact. *BMJ Global Health* 2017;**2**(2):e000212.

Kleinschmidt 2018

Kleinschmidt I, Bradley J, Knox TB, Mnzava AP, Kafy HT, Mbogo C, et al. Implications of insecticide resistance for malaria vector control with long-lasting insecticidal nets: a WHO-coordinated, prospective, international, observational cohort study. *Lancet Infectious Diseases* 2018;**18**(6):640-9.

Kroeger 1997

Kroeger A, Gerhardus A, Kruger G, Mancheno M, Pesse K. The contribution of repellent soap to malaria control. *American Journal of Tropical Medicine and Hygiene* 1997;**56**(5):580-4.

Topical repellents for malaria prevention (Review)

Maia 2011

Maia MF, Moore SJ. Plant-based insect repellents: a review of their efficacy, development and testing. *Malaria Journal* 2011;**10**(Suppl 1):S11.

Maia 2013

Maia MF, Onyango SP, Thele M, Simfukwe ET, Turner EL, Moore SJ. Do topical repellents divert mosquitoes within a community? Health equity implications of topical repellents as a mosquito bite prevention tool. *PLoS One* 2013;**8**(12):e84875.

Maia 2018

Maia MF, Kliner M, Richardson M, Lengeler C, Moore SJ. Mosquito repellents for malaria prevention. *Cochrane Database of Systematic Reviews* 2018, Issue 2. Art. No: CD011595. [DOI: [10.1002/14651858.CD011595.pub2](https://doi.org/10.1002/14651858.CD011595.pub2)]

Messenger 2023

Messenger LA, Furnival-Adams J, Chan K, Pelloquin B, Paris L, Rowland M. Vector control for malaria prevention during humanitarian emergencies: a systematic review and meta-analysis. *Lancet Global Health* 2023;**11**(4):e534-45. [DOI: [10.1016/S2214-109X\(23\)00044-X](https://doi.org/10.1016/S2214-109X(23)00044-X)]

Nguyen 2023

Nguyen QD, Vu MN, Hebert AA. Insect repellents: an updated review for the clinician. *Journal of the American Academy of Dermatology* January 2023;**88**(1):123-30. [DOI: [10.1016/j.jaad.2018.10.053](https://doi.org/10.1016/j.jaad.2018.10.053)]

Norris 2017

Norris EJ, Coets JR. Current and future repellent technologies: the potential of spatial repellents and their place in mosquito-borne disease control. *International Journal of Environmental Research and Public Health* 2017;**14**(2):124. [DOI: [10.3390/ijerph14020124](https://doi.org/10.3390/ijerph14020124)]

Ochomo 2023

Ochomo EO, Milanoi S, Abong'o B, Onyango B, Muchoki M, Omoke D, et al. Molecular surveillance leads to the first detection of *Anopheles stephensi* in Kenya. Preprint version 1. Research Square (posted 21 January 2023). [DOI: [10.21203/rs.3.rs-2498485/v1](https://doi.org/10.21203/rs.3.rs-2498485/v1)]

Olapeju 2021

Olapeju B, Adams C, Hunter G, Wilson S, Simpson J, Mitchum L, et al. Malaria prevention and care seeking among gold miners in Guyana. *PLoS One* 2021;**15**(12):e0244454.

Ranjha 2021

Ranjha R, Sharma A. Forest malaria: the prevailing obstacle for malaria control and elimination in India. *BMJ Global Health* 2021;**6**(5):e005391. [DOI: [10.1136/bmjgh-2021-005391](https://doi.org/10.1136/bmjgh-2021-005391)]

RevMan Web 2023 [Computer program]

Review Manager Web (RevMan Web). Version 4.26.0. The Cochrane Collaboration, 2023. Available at revman.cochrane.org.

Rowland 2001

Rowland M. Refugee health in the tropics. Malaria control in Afghan refugee camps: novel solutions. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2001;**95**(2):125-6.

Rowland 2004

Rowland M, Downey G, Rab A, Freeman T, Mohammad N, Rehman H, et al. DEET mosquito repellent provides personal protection against malaria: a household randomized trial in an Afghan refugee camp in Pakistan. *Tropical Medicine & International Health* 2004;**9**(3):335-42.

Russell 2011

Russell TL, Govella NJ, Azizi S, Drakeley CJ, Kachur SP, Killeen GF. Increased proportions of outdoor feeding among residual malaria vector populations following increased use of insecticide-treated nets in rural Tanzania. *Malaria Journal* 2011;**10**:80. [DOI: [10.1186/1475-2875-10-80](https://doi.org/10.1186/1475-2875-10-80)]

Saavedra 2019

Saavedra MP, Conn JE, Alava F, Carrasco-Escobar G, Prussing C, Bickersmith SA, et al. Higher risk of malaria transmission outdoors than indoors by *Nyssorhynchus darlingi* in riverine communities in the Peruvian Amazon. *Parasites and Vectors* 2019;**12**(1):374. [DOI: [10.1186/s13071-019-3619-0](https://doi.org/10.1186/s13071-019-3619-0)]

Sangoro 2014

Sangoro O, Kelly AH, Mtali S, Moore SJ. Feasibility of repellent use in a context of increasing outdoor transmission: a qualitative study in rural Tanzania. *Malaria Journal* 2014;**13**:347.

Semakula 2023

Semakula HM, Liang S, Mukwaya PI, Mugagga F, Swahn M, Nseka D, et al. Determinants of malaria infections among children in refugee settlements in Uganda during 2018-2019. *Infectious Diseases of Poverty* 2023;**12**(1):31. [DOI: [10.1186/s40249-023-01090-3](https://doi.org/10.1186/s40249-023-01090-3)]

Sinka 2012

Sinka ME, Bangs MJ, Manguin S, Rubio-Palis Y, Chareonviriyaphap T, Coetzee M, et al. A global map of dominant malaria vectors. *Parasites & Vectors* 2012;**5**:69.

Sinka 2020

Sinka ME, Pironon S, Massey NC, Longbottom J, Hemingway J, Moyes CL, et al. A new malaria vector in Africa: predicting the expansion range of *Anopheles stephensi* and identifying the urban populations at risk. *Proceedings of the National Academy of Sciences of the United States of America* 2020;**117**(40):24900-8.

Steinhardt 2017

Steinhardt LC, Jean YS, Impoinvil D, Mace KE, Wiegand R, Huber CS, et al. Effectiveness of insecticide-treated bednets in malaria prevention in Haiti: a case-control study. *Lancet Global Health* 2017;**5**(1):e96-103.

Sterne 2016

Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions. *BMJ* 2016;**355**:i4919.

Sterne 2019

Sterne JA, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;**366**:l4898. [DOI: [10.1136/bmj.l4898](https://doi.org/10.1136/bmj.l4898)]

UNHCR 2022

United Nations High Commissioner for Refugees. Guidance note on malaria programs in refugee operations. June 2022. [unhcr.org/sites/default/files/legacy-pdf/53ba5cca9.pdf](https://www.unhcr.org/sites/default/files/legacy-pdf/53ba5cca9.pdf) (accessed 1 January 2023).

Unwin 2023

Unwin HJT, Sherrard-Smith E, Churcher TS, Ghani AC. Quantifying the direct and indirect protection provided by insecticide treated bed nets against malaria. *Nature Communications* 2023;**14**(1):676. [DOI: [10.1038/s41467-023-36356-9](https://doi.org/10.1038/s41467-023-36356-9)]

Vythilingam 2021

Vythilingam I, Chua TH, Liew JW, Manin BO, Ferguson HM. The vectors of *Plasmodium knowlesi* and other simian malarias Southeast Asia: challenges in malaria elimination. *Advances in Parasitology* 2021;**113**:131-89.

WHO 2015

World Health Organization. Global technical strategy for malaria 2016-2030. Available at [who.int/docs/default-source/documents/global-technical-strategy-for-malaria-2016-2030.pdf?sfvrsn=c82afcc_0](https://www.who.int/docs/default-source/documents/global-technical-strategy-for-malaria-2016-2030.pdf?sfvrsn=c82afcc_0) (accessed 20 May 2021).

WHO 2020a

World Health Organization. World Malaria Report 2020. Available at [who.int/publications/i/item/9789240015791](https://www.who.int/publications/i/item/9789240015791) (accessed 20 May 2021).

WHO 2021

World Health Organization Global Malaria Program. WHO guidelines for malaria; 2021. Available at [who.int/publications/i/item/guidelines-for-malaria](https://www.who.int/publications/i/item/guidelines-for-malaria) (accessed 10 June 2022).

WHO 2022

World Health Organization. World Malaria Report 2022. Available at [who.int/teams/global-malaria-programme/reports/world-malaria-report-2022](https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2022) (accessed 15 January 2023).

WHO 2023a

World Health Organization. Vector control products targeting outdoor malaria transmission. 4 April 2023. Available at [who.int/publications/i/item/9789240072251](https://www.who.int/publications/i/item/9789240072251) (accessed 6 June 2023).

WHO 2023b

World Health Organization Global Malaria Program. WHO guidelines for malaria. 14 March 2023. Available at [who.int/publications/i/item/guidelines-for-malaria](https://www.who.int/publications/i/item/guidelines-for-malaria) (accessed 6 June 2023).

Wilson 2014

Wilson AL, Chen-Hussey V, Logan JG, Lindsay SW. Are topical insect repellents effective against malaria in endemic populations? A systematic review and meta-analysis. *Malaria Journal* 2014;**13**:446. [DOI: [10.1186/1475-2875-13-446](https://doi.org/10.1186/1475-2875-13-446)]

References to other published versions of this review
Wagah 2022

Wagah MG, Gabaldón-Figueira JC, Maia MF. Topical repellents for malaria prevention. *Cochrane Database of Systematic Reviews* 2022, Issue 1. Art. No: CD015422. [DOI: [10.1002/14651858.CD015422](https://doi.org/10.1002/14651858.CD015422)]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES
Characteristics of included studies [ordered by study ID]

Agius 2020
Study characteristics

| | |
|--------------|--|
| Methods | cRCT (stepped-wedge) Unit of randomization: clusters of villages ICC: 0.15 Trial duration: approximately 15 months |
| Participants | Adults or children living in malaria-endemic regions High-risk population (forest workers) Endemic region for <i>P vivax</i> |

Topical repellents for malaria prevention (Review)

Agius 2020 (Continued)

| | |
|---------------|---|
| | Participants not screened for hypnozoites |
| Interventions | <p>Topical repellent: 12% N, N-diethylbenzamide cream</p> <p>Controls: no intervention</p> <p>Co-interventions: LLINs</p> <p>Treatment arms:</p> <ul style="list-style-type: none"> since this was a stepped wedge trial, all clusters moved from control to intervention. There were 14 clusters (116 villages, approx. 31,016 people) |
| Outcomes | <ul style="list-style-type: none"> Malaria prevalence 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) Adherence to regular usage of the intervention (defined based on recommendations provided by researchers to participants of individual trials) |
| Notes | <p>Malaria case incidence is mentioned as an outcome in the paper, but not reported</p> <p>Carried out in Myanmar</p> <p>Funded by: Three Millennium Development Goal, Australian Research Council, Australian Centre for Research Excellence in Malaria Elimination</p> |

Chen-Hussey 2013

Study characteristics

| | |
|---------------|---|
| Methods | <p>cRCT</p> <p>Unit of randomization: cluster of houses</p> <p>ICC: not reported</p> <p>Trial duration: 1.5 years (average of 6.4 months follow-up per cluster)</p> |
| Participants | <p>Adults or children living in malaria-endemic regions</p> <p>High risk population (agricultural workers sleeping outdoors)</p> <p>Endemic region for <i>P vivax</i></p> <p>Participants not screened for hypnozoites</p> |
| Interventions | <p>Topical repellent: DEET 15%</p> <p>Controls: placebo lotion</p> <p>Co-interventions: LLINs</p> <p>Treatment arms:</p> <ul style="list-style-type: none"> Repellent arm: 795 households; 3972 participants Placebo arm: 802 households; 4008 participants |
| Outcomes | <ul style="list-style-type: none"> Malaria infection incidence: new <i>Plasmodium spp.</i> infections confirmed through thick or thin blood smears, RDTs, or polymerase chain reaction (PCR) |

Topical repellents for malaria prevention (Review)

Chen-Hussey 2013 (Continued)

- 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)
- Time to first infection (days)
- Adherence to regular usage of the intervention (defined based on recommendations provided by researchers to participants of individual trials)

Notes

Conducted in Laos PDR

Funded by the Department of Homeland Security, and Fogarty International Center, National Institutes of Health

Gryseels 2015
Study characteristics

Methods

 Sub-analysis of [Sluydts 2016](#) (see main study for methods)

Participants

 Sub-analysis of [Sluydts 2016](#) (see main study for participant description)

Interventions

 Sub-analysis of [Sluydts 2016](#) (see main study for intervention description)

Outcomes

Adherence to regular usage of the intervention (defined based on recommendations provided by researchers to participants of individual trials)

Notes

 This paper reports the adherence to repellent use from participants recruited to the [Sluydts 2016](#) trial.

Carried out in Cambodia

Funded by: Bill and Melinda Gates foundation, Belgian Cooperation

Hill 2007
Study characteristics

Methods

cRCT

Unit of randomization: cluster of houses

ICC: not reported

Trial duration: 7 months (treatment period of 4 months)

Participants

Adults or children living in malaria-endemic regions

Non-high risk population

 Endemic region for *P vivax*

Participants not screened for hypnozoites

Interventions

Topical repellent: PMD: 30% + eucalyptus extract

Controls: placebo lotion (0.1% clove oil used as placebo)

Topical repellents for malaria prevention (Review)

Hill 2007 (Continued)

| | |
|----------|--|
| | Co-interventions: LLINs |
| | Treatment arms: <ul style="list-style-type: none"> Intervention: 424 households (1967 individuals) Control: 436 households (2041 individuals) |
| Outcomes | <ul style="list-style-type: none"> Malaria infection incidence: new <i>Plasmodium</i> spp. infections confirmed through thick or thin blood smears, RDTs, or polymerase chain reaction (PCR) 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). All-cause fever Adherence to regular usage of the intervention (defined based on recommendations provided by researchers to participants of individual trials) |
| Notes | <p>Carried out in Bolivia</p> <p>Funded by Gates Malaria Partnership grant from London School of Hygiene and Tropical Medicine</p> |

Kroeger 1997

Study characteristics

| | |
|---------------|--|
| Methods | <p>cRCT</p> <p>Unit of randomization: villages</p> <p>ICC: not reported</p> <p>Trial duration: 7 months (treatment period of 6 months)</p> |
| Participants | <p>Adults or children living in malaria-endemic regions</p> <p>Non-high risk population</p> <p>Endemic region for <i>P vivax</i></p> <p>Participants not screened for hypnozoites</p> |
| Interventions | <p>Topical repellent: soap with 0.5% DEET and 20% permethrin</p> <p>Controls: no intervention</p> <p>Co-interventions: none</p> <p>Treatment arms: <ul style="list-style-type: none"> Intervention: 9 communities (total population not reported) Control: 9 villages (total population not reported) </p> |
| Outcomes | <ul style="list-style-type: none"> 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) Adherence to regular usage of the intervention (defined based on recommendations provided by researchers to participants of individual trials) Human biting rate (HBR) |

Kroeger 1997 (Continued)

| | |
|-------|---|
| Notes | Malaria case incidence was listed as an outcome, but it was self-reported, and raw data for this outcome is not presented |
| | Carried out in Ecuador and Peru |
| | Funded by: Commission of European Communities, Catholic Organization for Development |

McGready 2001

Study characteristics

| | |
|---------------|---|
| Methods | RCT Trial duration: 17 months (treatment period: 18 weeks) |
| Participants | Adults or children living in malaria-endemic regions (women 3 to 7 months pregnant) High-risk population (refugees) Endemic region for <i>P vivax</i> Participants not screened for hypnozoites |
| Interventions | Topical repellent: 20% DEET added to Thanaka (popular local cosmetic) Controls: Thanaka alone Co-intervention: none Treatment arms: <ul style="list-style-type: none"> Intervention: 449 Controls: 448 |
| Outcomes | <ul style="list-style-type: none"> Malaria infection incidence: new <i>Plasmodium spp.</i> infections confirmed through thick or thin blood smears, RDTs, or polymerase chain reaction (PCR) 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) Adherence to regular usage of the intervention (defined based on recommendations provided by researchers to participants of individual trials) |
| Notes | Carried out in camps for displaced people of the Karen ethnic minority in Thailand Funded by the Danish Bilharziasis Laboratory and was part of the Wellcome-Mahidol University of Oxford Tropical Medicine Research Programme funded by the Wellcome Trust |

Rowland 2004

Study characteristics

| | |
|---------|--|
| Methods | cRCT Unit of randomization: cluster of households |
|---------|--|

Topical repellents for malaria prevention (Review)

Rowland 2004 (Continued)

| | |
|---------------|---|
| | ICC: 0.04 |
| | Trial duration: 7 months (treatment period of 6 months) |
| Participants | <p>Adults or children living in malaria-endemic regions</p> <p>High-risk population (refugees)</p> <p>Endemic region for <i>P vivax</i></p> <p>Participants not screened for hypnozoites</p> |
| Interventions | <p>Topical repellent: Mosbar soap (20% DEET + 0.5% permethrin)</p> <p>Controls: placebo lotion</p> <p>Co-interventions: none</p> <p>Treatment arms:</p> <ul style="list-style-type: none"> • Intervention: 67 households (618 participants) • Controls: 60 households (530 participants) |
| Outcomes | <ul style="list-style-type: none"> • 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 • Adherence to regular usage of the intervention (defined based on recommendations provided by researchers to participants of individual trials) |
| Notes | <p>Carried out in a refugee camp with Afghan refugees in malaria-endemic region of Pakistan</p> <p>Funded by HealthNet International's Malaria and Leishmaniasis control and research programme</p> |

Sangoro 2014a
Study characteristics

| | |
|---------------|---|
| Methods | <p>cRCT</p> <p>Unit of randomization: cluster of households</p> <p>ICC: not reported</p> <p>Trial duration: 14 months</p> |
| Participants | <p>Adults or children living in malaria endemic regions</p> <p>Non-high risk population</p> |
| Interventions | <p>Topical repellent: 15% DEET lotion</p> <p>Controls: placebo lotion</p> <p>Co-interventions: LLINs</p> <p>Treatment arms:</p> <ul style="list-style-type: none"> - Intervention: 10 clusters, 468 households and 2224 participants |

Topical repellents for malaria prevention (Review)

Sangoro 2014a (Continued)

- Controls: 10 clusters, 469 households and 2202 participants

Outcomes

- Malaria case incidence: new cases of clinical malaria (caused by *Plasmodium spp.*) confirmed through blood smears or RDTs

- Adherence to regular usage of the intervention (defined based on recommendations provided by researchers to participants of individual trials)

Notes

Carried out in Tanzania.

Funded by Population Services International.

Sluydts 2016
Study characteristics
Methods

cRCT

Unit of randomization: cluster made up by individual villages or a group of closely located villages

ICC: not reported, retrospectively calculated: 0.0294

Trial duration: 20 months

Participants

Adults or children living in malaria endemic regions

High risk population (forest workers)

Endemic region for *P vivax*

Participants not screened for hypnozoites

Interventions

Topical repellent: picaridin (KBR3023)

Controls: no treatment

Picaridin 10% for children < 10 years, and Picaridin 20% in individuals ≥ 10 years

Co-interventions: LLINs

Treatment arms:

- Intervention: 49 clusters, 57 villages (5642 households, 25,051 individuals)
- Controls: 49 clusters, 56 villages (5287 households, 23,787 individuals)

Outcomes

• Malaria case incidence: new cases of clinical malaria (caused by *Plasmodium spp.*) confirmed through blood smears or RDTs

• 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

• Adherence to regular usage of the intervention (defined based on recommendations provided by researchers to participants of individual trials)

Notes

Carried out in Cambodia

Funded by: Bill and Melinda Gates Foundation, Belgian Cooperation

cRCT: cluster-randomized controlled trial; ICC: intra-class correlation coefficient; LLIN: long-lasting insecticide-treated nets; RDTs: rapid diagnostic tests

Characteristics of excluded studies [ordered by study ID]

| Study | Reason for exclusion |
|----------------------------------|--|
| Constantini 2004 | Inadequate study design; this study is an entomologic trial and does not evaluate the effect of repellents on epidemiological outcomes |
| Dadzie 2013 | The study does not comply with the inclusion criteria for CBA (only one site per arm) |
| Deressa 2014 | The characteristics of the repellent were not properly described |
| Lindsay 1998 | This study is an entomological and acceptability study not measuring malaria epidemiological outcomes. |
| Maia 2012 | The study is an entomological evaluation and does not report outcomes included in this review. |
| Moore 2007 | This study is an entomological evaluation not measuring malaria epidemiological outcomes |
| Rowland 2004b | Inadequate study design; the paper reports a case-control study. |
| Uzzan 2009 | This study is an entomological evaluation, and does not measure malaria epidemiological outcomes |

Abbreviations: CBA: controlled before-after study; RCT: randomized controlled trial

Characteristics of ongoing studies [ordered by study ID]

[NCT02938975](#)

| | |
|---------------------|--|
| Study name | Field efficacy of insecticide treated uniforms and skin repellents for malaria prevention (URCT) |
| Methods | Cluster-RCT using a 4-arm non-inferiority design with 12 months of follow-up |
| Participants | Healthy recruits of the Tanzanian National Service Program JKT Mgambo Camp |
| Interventions | Ultra 30 insect repellent lotion (30% Lipo DEET) in combination or not with permethrin factory-treated army combat uniforms |
| Outcomes | The primary epidemiological outcome will be the incidence of <i>P falciparum</i> malaria through monthly measurement of malaria positivity by direct polymerase chain reaction (PCR) to detect parasite DNA. |
| Starting date | November 2017 |
| Contact information | Sarah Moore (smoore@ihi.or.tz) |
| Notes | clinicaltrials.gov/ct2/show/record/NCT02938975 |

NCT05117567

| | |
|---------------|--|
| Study name | Reducing malaria transmission in forest-going mobile and migrant populations in Lao PDR and Cambodia |
| Methods | Stepped-wedge cluster-randomized controlled trial (one-way crossover) with nested mixed methods study. Open label study |
| Participants | <p>Mobile and migrant individuals aged 18 years and over in selected villages including:</p> <ul style="list-style-type: none"> • Traditional slash-and-burn and paddy field farming communities visiting their forest farms (commonly ethnic minority groups) • Seasonal agricultural labourers • Forest workers in the informal sector (hunters, small-scale gem/gold miners, people gathering forest products (precious timber, construction timber, rattan/bamboo) • Transient or mobile camp residents associated with commercial projects (road/pipeline construction, large-scale logging, deep seaport projects, etc.) • Formal and informal cross-border migrant workers <p>For qualitative research component, local health stakeholders meeting the following criteria will be eligible:</p> <ul style="list-style-type: none"> • Aged 18 years and over • The local health stakeholders, such as health centre staff, Operational District Malaria Supervisor (ODMS), and Provincial Malaria Supervisor (PMS), and basic health staff, such as malaria unit staff in health centres, midwives, health assistants, district health officers and district focal person from CMPE and CNM • Health staff members from HPA and Lao malaria community service organizations <p>Estimated enrolment: 5868 participants</p> |
| Interventions | <p>Combination product: personal protection package</p> <p>A personal protection package that includes long-lasting insecticidal hammock net (LLIHN), insect repellent (Icaridin), and MMP-tailored behavioural change communication (BCC) package</p> |
| Outcomes | <p>Primary outcomes</p> <ul style="list-style-type: none"> • <i>Plasmodium</i> spp. infection diagnosed by RDT (time frame: assessed weekly, longitudinally over 12 months) <p>Change in the number of <i>Plasmodium</i> spp. infections detected by RDT per week per village</p> <p>Secondary outcomes</p> <ul style="list-style-type: none"> • Symptomatic malaria diagnosed by RDT (time frame: assessed weekly, longitudinally over 12 months) <p>Change in the number of symptomatic <i>Plasmodium</i> spp. infections detected by RDT per week per village.</p> <ul style="list-style-type: none"> • <i>Plasmodium</i> spp. infection, determined by polymerase chain reaction (PCR) on RDT cassette samples (time frame: assessed weekly, longitudinally over 12 months) <p>Change in the prevalence of <i>Plasmodium</i> spp. infection, determined by polymerase chain reaction (PCR) from RDT cassette samples</p> <ul style="list-style-type: none"> • <i>Plasmodium</i> spp. infection, determined by polymerase chain reaction (PCR) on dried blood spot samples (time frame: assessed weekly, longitudinally over 12 months) <p>Change in the prevalence of <i>Plasmodium</i> spp. infection, determined by polymerase chain reaction (PCR) from dried blood spot (DBS) samples</p> |

NCT05117567 (Continued)

- *Plasmodium* spp. infections with drug resistance mutations (time frame: assessed weekly, longitudinally over 12 months)

Change in the prevalence of *Plasmodium* spp. infection with drug resistance mutations

- Prevalence of antibodies to *Plasmodium* spp. (time frame: assessed weekly, longitudinally over 12 months)

Prevalence of antibodies to *Plasmodium* spp., determined by enzyme-linked immunosorbent assay (ELISA), from RDT and DBS samples

- Levels of antibodies to *Plasmodium* spp. (time frame: assessed weekly, longitudinally over 12 months)

Levels of antibodies to *Plasmodium* spp., determined by ELISA, from RDT and DBS samples

- Prevalence of antibodies to vector salivary antigens (time frame: assessed weekly, longitudinally over 12 months)

Levels of antibody biomarkers of vector exposure

- Levels of antibodies to vector salivary antigens (time frame: assessed weekly, longitudinally over 12 months)

Levels of antibody biomarkers of vector exposure

- Levels of knowledge, attitude, and practice regarding malaria prevention among MMPs (time frame: at approximately 12 months)

Focus group discussions

- Proportion of survey respondents (MMPs) who accept and are willing to use/did use the personal protection package according to the protocol (time frame: at approximately 12 months)

Starting date 01 December 2021

Contact information Freya JI Fowkes: +613 8506 2310
freya.fowkes@burnet.edu.au

Notes

Abbreviations: PCR: polymerase chain reaction; RCT: randomized controlled trial.

RISK OF BIAS

Legend:  Low risk of bias  High risk of bias  Some concerns

Risk of bias for analysis 1.3 Malaria incidence (by risk population)

| Study | Bias | | | | | Overall |
|--|-----------------------|--|----------------------|----------------------------|-----------------------------------|---------|
| | Randomisation process | Deviations from intended interventions | Missing outcome data | Measurement of the outcome | Selection of the reported results | |
| Subgroup 1.3.1 High-risk population | | | | | | |

| Study | Bias | | | | | Overall |
|--|-----------------------|--|----------------------|----------------------------|-----------------------------------|---------|
| | Randomisation process | Deviations from intended interventions | Missing outcome data | Measurement of the outcome | Selection of the reported results | |
| Chen-Hussey 2013 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| McGready 2001 | ~ | ✓ | ✗ | ✓ | ~ | ✗ |
| Sluydts 2016 | ~ | ~ | ✓ | ✓ | ✓ | ~ |
| Subgroup 1.3.2 Non-high risk population | | | | | | |
| Hill 2007 | ✗ | ✓ | ✓ | ✓ | ✓ | ✗ |

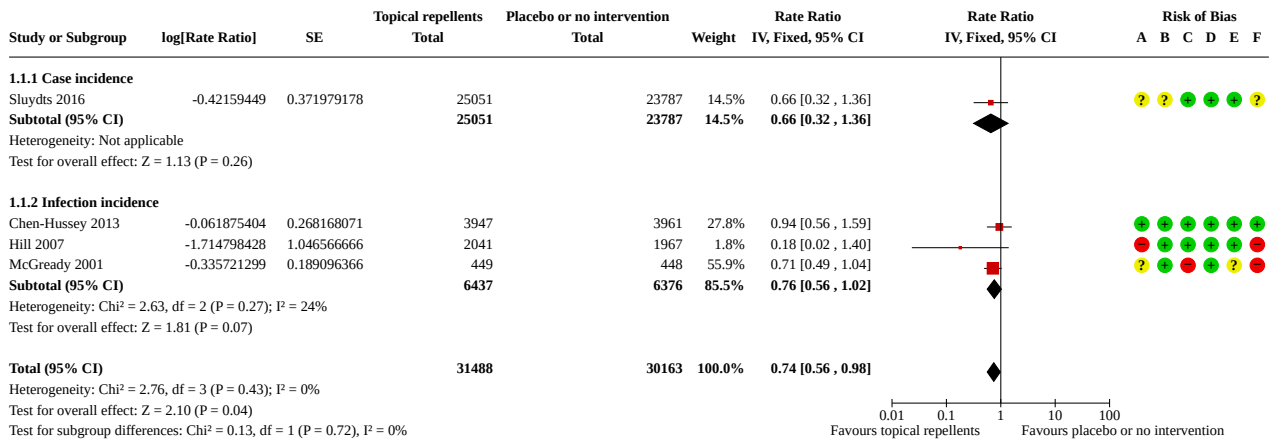
DATA AND ANALYSES

Comparison 1. Topical repellents versus placebo or no intervention

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|----------------|---------------------|--------------------------------|-------------------|
| 1.1 Malaria incidence (case and infection) | 4 | 61651 | Rate Ratio (IV, Fixed, 95% CI) | 0.74 [0.56, 0.98] |
| 1.1.1 Case incidence | 1 | 48838 | Rate Ratio (IV, Fixed, 95% CI) | 0.66 [0.32, 1.36] |
| 1.1.2 Infection incidence | 3 | 12813 | Rate Ratio (IV, Fixed, 95% CI) | 0.76 [0.56, 1.02] |
| 1.2 Malaria incidence (use of other interventions) | 4 | 61651 | Rate Ratio (IV, Fixed, 95% CI) | 0.74 [0.56, 0.98] |
| 1.2.1 Use of bednets and other interventions | 3 | 60754 | Rate Ratio (IV, Fixed, 95% CI) | 0.78 [0.51, 1.18] |
| 1.2.2 Without use of bednets and other interventions | 1 | 897 | Rate Ratio (IV, Fixed, 95% CI) | 0.71 [0.49, 1.04] |
| 1.3 Malaria incidence (by risk population) | 4 | 61651 | Rate Ratio (IV, Fixed, 95% CI) | 0.74 [0.56, 0.98] |
| 1.3.1 High-risk population | 3 | 57643 | Rate Ratio (IV, Fixed, 95% CI) | 0.76 [0.58, 1.01] |
| 1.3.2 Non-high risk population | 1 | 4008 | Rate Ratio (IV, Fixed, 95% CI) | 0.18 [0.02, 1.40] |
| 1.4 Reported adverse events in the topical repellents arm of included studies | 0 | | Other data | No numeric data |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|--|----------------|---------------------|---------------------------------|-------------------|
| 1.5 Malaria prevalence | 4 | 55366 | Odds Ratio (IV, Fixed, 95% CI) | 0.81 [0.67, 0.97] |
| 1.5.1 No refugees | 2 | 53321 | Odds Ratio (IV, Fixed, 95% CI) | 0.90 [0.73, 1.11] |
| 1.5.2 Refugees | 2 | 2045 | Odds Ratio (IV, Fixed, 95% CI) | 0.61 [0.44, 0.86] |
| 1.6 Malaria prevalence (per-protocol analysis) | 2 | | Odds Ratio (IV, Fixed, 95% CI) | 0.81 [0.42, 1.56] |
| 1.7 Anaemia | 1 | 587 | Odds Ratio (M-H, Fixed, 95% CI) | 1.12 [0.81, 1.55] |
| 1.8 All-cause fever | 1 | 4008 | Rate Ratio (IV, Fixed, 95% CI) | 0.42 [0.32, 0.56] |
| 1.9 Adherence to the intervention | 0 | | Other data | No numeric data |

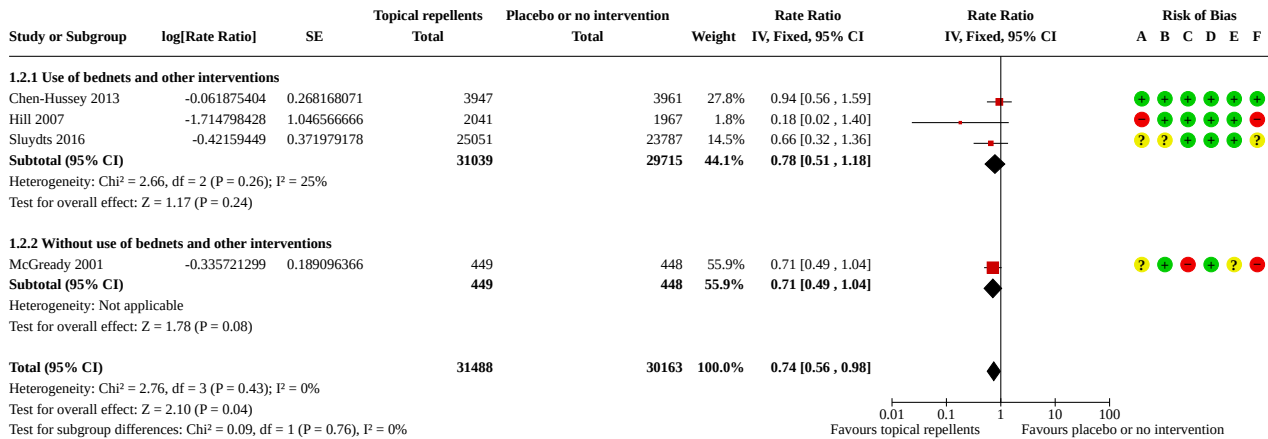
Analysis 1.1. Comparison 1: Topical repellents versus placebo or no intervention, Outcome 1: Malaria incidence (case and infection)



Risk of bias legend

- (A) Bias arising from the randomization process
- (B) Bias due to deviations from intended interventions
- (C) Bias due to missing outcome data
- (D) Bias in measurement of the outcome
- (E) Bias in selection of the reported result
- (F) Overall bias

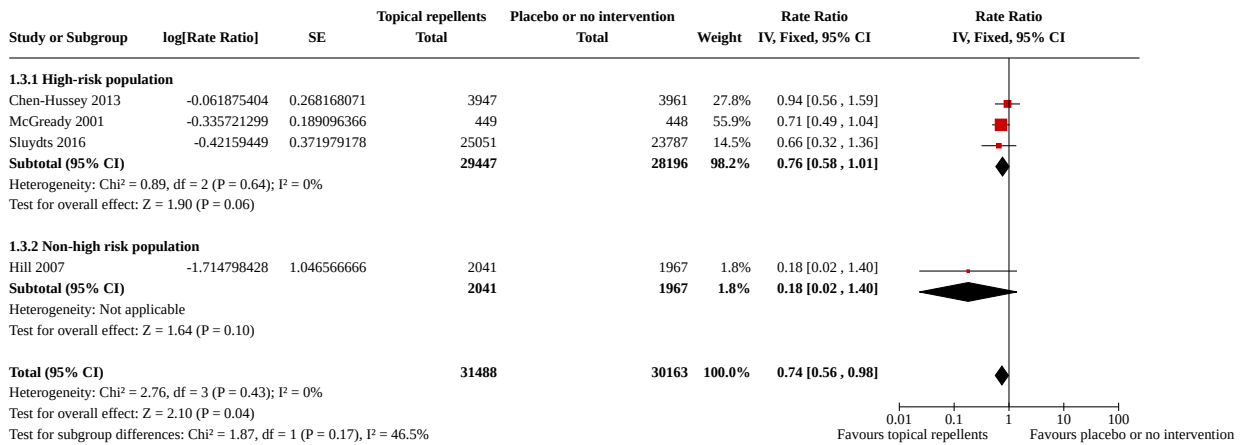
Analysis 1.2. Comparison 1: Topical repellents versus placebo or no intervention, Outcome 2: Malaria incidence (use of other interventions)



Risk of bias legend

- (A) Bias arising from the randomization process
- (B) Bias due to deviations from intended interventions
- (C) Bias due to missing outcome data
- (D) Bias in measurement of the outcome
- (E) Bias in selection of the reported result
- (F) Overall bias

Analysis 1.3. Comparison 1: Topical repellents versus placebo or no intervention, Outcome 3: Malaria incidence (by risk population)



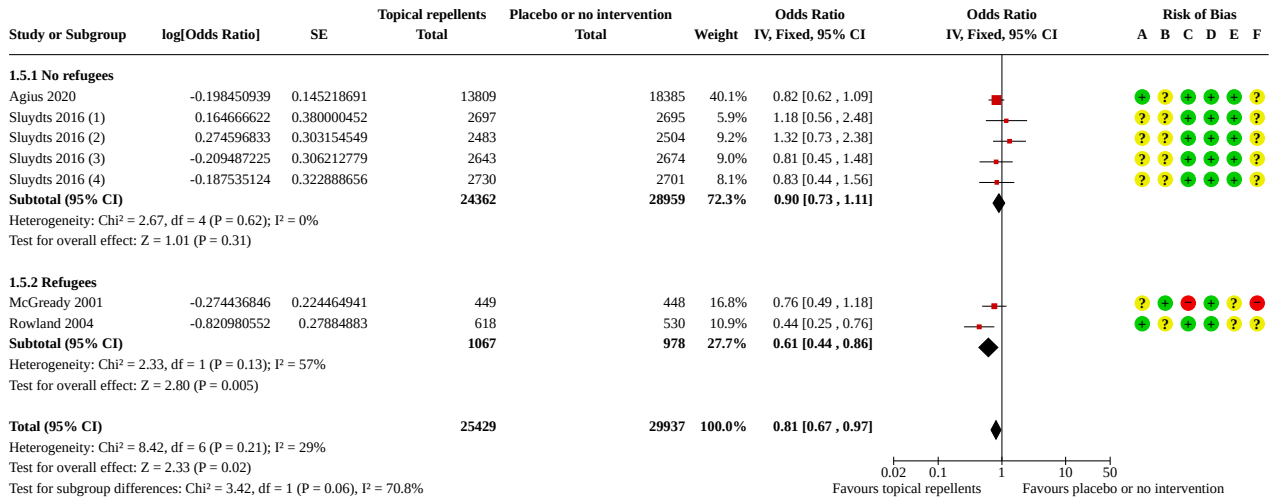
Analysis 1.4. Comparison 1: Topical repellents versus placebo or no intervention, Outcome 4: Reported adverse events in the topical repellents arm of included studies

Reported adverse events in the topical repellents arm of included studies

| Study | Total adverse events reported in the topical repellents arm | Population in the topical repellents arm | % |
|------------------|---|--|-------|
| Agius 2020 | 0 | 13809 | 0% |
| Chen-Hussey 2013 | 150 | 3947 | 3.8 |
| Hill 2007 | 0 | 2041 | 0% |
| Kroeger 1997 | 48 | 1600 | 3% |
| McGready 2001 | 51 | 449 | 11.4% |
| Rowland 2004 | 1 | 618 | 0.16% |
| Sluydts 2016 | 33 | 25051 | 0.13% |

Topical repellents for malaria prevention (Review)

Analysis 1.5. Comparison 1: Topical repellents versus placebo or no intervention, Outcome 5: Malaria prevalence



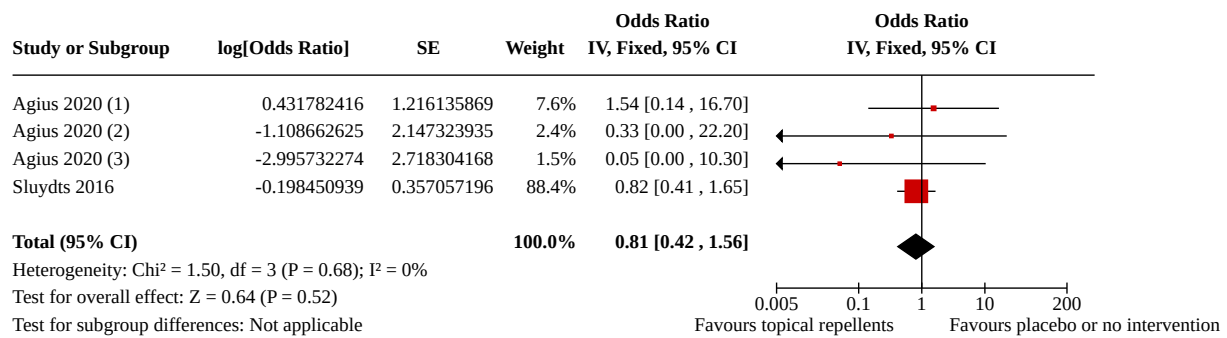
Footnotes

- (1) Survey 3
- (2) Survey 2
- (3) Survey 1
- (4) Survey 4

Risk of bias legend

- (A) Bias arising from the randomization process
- (B) Bias due to deviations from intended interventions
- (C) Bias due to missing outcome data
- (D) Bias in measurement of the outcome
- (E) Bias in selection of the reported result
- (F) Overall bias

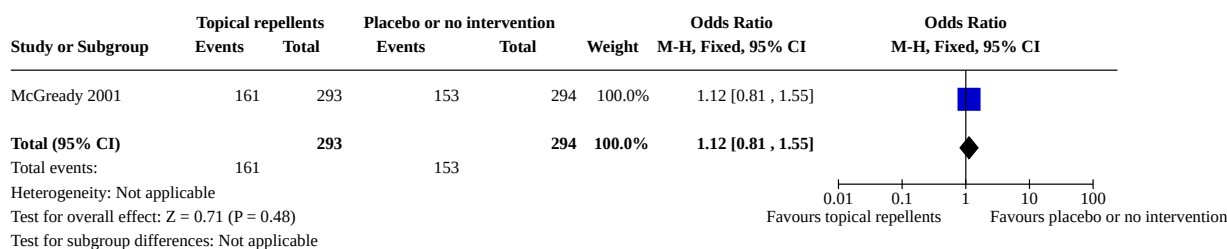
Analysis 1.6. Comparison 1: Topical repellents versus placebo or no intervention, Outcome 6: Malaria prevalence (per-protocol analysis)



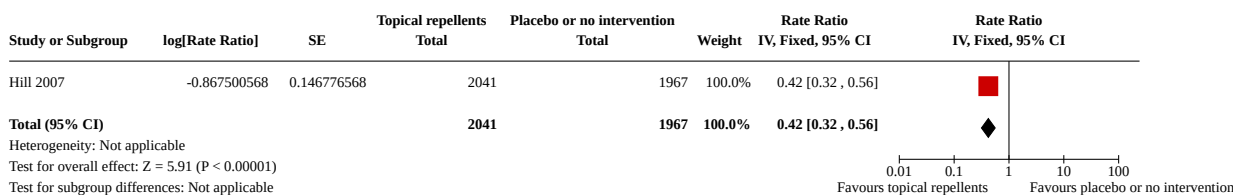
Footnotes

- (1) Participants who used the repellent monthly
- (2) Participants who used the repellent weekly
- (3) Participants who used the repellent daily

Analysis 1.7. Comparison 1: Topical repellents versus placebo or no intervention, Outcome 7: Anaemia



Analysis 1.8. Comparison 1: Topical repellents versus placebo or no intervention, Outcome 8: All-cause fever



Analysis 1.9. Comparison 1: Topical repellents versus placebo or no intervention, Outcome 9: Adherence to the intervention

Adherence to the intervention

| Study | Use % (self-reported) | Use % (Confirmed) |
|-------------------------|---|-------------------|
| Agius 2020 | NA | 56% |
| Chen-Hussey 2013 | 61.3% | 47.4% |
| Gryseels 2015 | 34% | 7.9% |
| Hill 2007 | NA | 98.5% |
| Kroeger 1997 | 81.9% coverage household members in Ecuador; 91.3% in Peru | |
| McGready 2001 | 90.5% | 84.6% |
| Rowland 2004 | 95% | NA |
| Sangoro 2014a | NA | 99.2% |
| Sluydts 2016 | 72% and 69% in successive surveys | NA |

ADDITIONAL TABLES

Table 1. Reported adverse events in the topical repellents arm of included studies (Analysis 1.4)

| Study | Total adverse events reported in the topical repellents arm | Study population in the topical repellents arm | % |
|--|---|--|-----|
| Agius 2020 | 0 | 13809 | 0 |
| Chen-Hussey 2013^a | 150 | 3947 | 3.8 |
| Hill 2007 | 0 | 2041 | 0 |
| Kroeger 1997 | 48 | 1600 | 3 |

Table 1. Reported adverse events in the topical repellents arm of included studies (Analysis 1.4) (Continued)

| | | | |
|---------------|------------|--------------|------------|
| McGready 2001 | 51 | 449 | 11.4 |
| Rowland 2004 | 1 | 618 | 0.16 |
| Sluydts 2016 | 33 | 25051 | 0.13 |
| Total | 283 | 47515 | 0.6 |

^aStudies that reported adverse events in both intervention arms

Table 2. Adherence to the intervention (Analysis 1.9)

| Study | Regular use % (self-reported) | Regular use % (observed) ^a |
|----------------------------|--------------------------------|---------------------------------------|
| Agius 2020 | NA | 56 |
| Chen-Hussey 2013 | 61.3 | 47.4 |
| Gryseels 2015 ^b | 34 | 7.9 |
| Hill 2007 | NA | 98.5 |
| Kroeger 1997 | 81.9 (Ecuador), 91.3 (Peru) | NA |
| McGready 2001 | 90.5 | 84.6 |
| Rowland 2004 | 95 | NA |
| Sangoro 2014a | NA | 99.2 ^c |
| Sluydts 2016 ^b | 72 and 69 (successive surveys) | NA |

^aMeasured using different strategies:

Agius 2020 reported by individual village health workers at the village level; details not provided

Chen-Hussey 2013 observed by carrying out random sniff-checks

Hill 2007 observed by carrying out sniff-checks

McGready 2001 observed via random house visits, not specified

^bGryseels 2015 and Sluydts 2016 report results from the same study, but Sluydts 2016 only measured adherence based on usage the night before the survey, while Gryseels 2015 evaluated usage throughout the whole study period. The determination of observed adherence in this study also included unannounced visits to randomly selected houses to perform sniff checks and observe the correct application of the repellent.

^cSangoro 2014a estimated based on the number of participants included in the per-protocol analysis (PPA), compared to the intention-to-treat (ITT).

APPENDICES

Appendix 1. Detailed search strategies for electronic databases

CENTRAL

Issue 1 of 12, January 2023

#1 malaria

Topical repellents for malaria prevention (Review)

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#2 (vector or vectors or mosquito or anopheles):ti,ab,kw

#3 MeSH descriptor: [Insect Vectors] explode all trees

#4 MeSH descriptor: [Insect Bites and Stings] explode all trees

#5 #2 or #3 or #4

#6 #1 and #5

#7 MeSH descriptor: [Mosquito Control] explode all trees

#8 #6 or #7

#9 MeSH descriptor: [Insect Repellents] explode all trees

#10 (repel*):ti,ab,kw

#11 (("Insecticide treated clothing" or ITC)):ti,ab,kw

#12 lotion* or gel or gels

#13 wipe* or soap* or cream*

#14 roll-on

#15 #9 or #10 or #11 or #12 or #13

#16 #15 and #8

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

Embase 1947-Present, updated daily

1 Malaria/

2 malaria.tw.

Topical repellents for malaria prevention (Review)

- 3 1 or 2
- 4 insect vector/
- 5 vector*.tw.
- 6 mosquito*.mp. or mosquito vector/
- 7 Anopheles/ or anopheles.tw.
- 8 Insect Bite/ or insect sting/
- 9 4 or 5 or 6 or 7 or 8
- 10 3 and 9
- 11 Mosquito Control/
- 12 10 or 11
- 13 insect repellent/
- 14 topical repel*.tw.
- 15 repellent*.tw.
- 16 ("Insecticide treated clothing" or ITC).tw.
- 17 (lotion* or gel or gels or roll-on* or wipe* or soap* or cream*).tw.
- 18 (Spray* and skin).mp.
- 19 personal protection.mp.
- 20 13 or 14 or 15 or 16 or 17 or 18 or 19
- 21 12 and 20
- 22 (random* or factorial* or placebo* or assign* or allocat* or crossover*).tw.
- 23 (control* adj group*).tw.
- 24 (trial* and (control* or comparative)).tw.
- 25 ((blind* or mask*) and (single or double or triple or treble)).tw.
- 26 (randomized or randomly or RTC).ab.
- 27 crossover procedure/ or double blind procedure/ or single blind procedure/
- 28 placebo/ or clinical trial/ or parallel design/ or Latin square design/
- 29 time series analysis/
- 30 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
- 31 21 and 30

LILACS

Search on: malaria vector\$ or mosquito\$ or anopheles [Words] and topical repellent\$ or personal repellent\$ or soap or lotion\$ or cream \$ or cloth\$ [Words]

CAB Abstracts (Web of Science)

#20 #19 AND #14

#19 #18 OR #17 OR #16 OR #15

Topical repellents for malaria prevention (Review)

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#18 ("Controlled Before-After" OR "Interrupted Time Series") (Abstract)

#17 randomized or placebo or randomly or trial or groups (Abstract)

#16 controlled clinical trial (Topic)

#15 randomized controlled trial (Topic)

#14 #13 AND #7

#13 #12 OR #11 OR #10 OR #9 OR #8

#12 personal near/2 protection (Topic)

#11 Spray* near/2 skin (Topic)

#10 (lotion* or gel or gels or roll-on* or wipe* or soap* or cream*) (Topic)

#9 ("Insecticide treated clothing" or ITC) (Topic)

#8 insect repellent* or topical repel* (Topic)

#7 #1 OR #6

#6 #5 AND #4

#5 malaria (Topic)

#4 #2 OR #3

#3 insect near/2 bite* (Topic)

#2 mosquito* or mosquito near/2 vector or anopheles (Topic)

#1 malaria near/2 vector* (Topic)

Clinicaltrials.gov; WHO ICTRP

mosquito* and repel*

US Armed Forces Pest Management Board

mosquito repellent*

French Institute of Research for Development's Horizon Pleins Textes

mosquito repellents

HISTORY

Protocol first published: Issue 1, 2022

CONTRIBUTIONS OF AUTHORS

JCGF, MGW, and MFM contributed to the design of the study.

All review authors contributed to the data extraction and analysis of the results.

All review authors contributed to the writing of the draft and definitive versions of the manuscript.

All review authors read and approved the final manuscript version prior to publication.

DECLARATIONS OF INTEREST

JCGF has no known conflicts of interest.

MGW has no known conflicts of interest.

LBA has no known conflicts of interest.

Topical repellents for malaria prevention (Review)

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CW has no known conflicts of interest.

MFM has no known conflicts of interest.

SOURCES OF SUPPORT

Internal sources

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External sources

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Project number 300342-104

- La Caixa Inphinit Fellowship, Spain

ID 100010434, fellowship code: LCF/BQ/DI21/11860037

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol, we presented malaria infection incidence and malaria case incidence exclusively as individual outcomes ([Wagah 2022](#)). Given the small number of studies included in the review, both outcomes were ultimately pooled and treated as a single outcome: malaria case and infection incidence. We performed a subgroup analysis separating both outcomes, and reported both the independent and pooled results in the summary of findings table. Since cluster-adjusted IRRs and ORs were directly extracted from studies reporting them, we did not use the design effect of the studies to estimate cluster effects. For the same reason, a sensitivity analysis using different estimated ICCs was not necessary.

INDEX TERMS

Medical Subject Headings (MeSH)

Controlled Before-After Studies; *Culicidae; *Insecticides; *Malaria, Falciparum; Mosquito Vectors

MeSH check words

Animals; Humans