Cochrane Library

Cochrane Database of Systematic Reviews

Insecticide space spraying for preventing malaria transmission (Protocol)

Pryce J, Choi L, Malone D

Pryce J, Choi L, Malone D.
Insecticide space spraying for preventing malaria transmission.
Cochrane Database of Systematic Reviews 2017, Issue 6. Art. No.: CD012689.
DOI: 10.1002/14651858.CD012689.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Protocol]

Insecticide space spraying for preventing malaria transmission

Joseph Pryce[1], Leslie Choi[1], David Malone[2]

[1]Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, UK. [2]IVCC, Liverpool School of Tropical Medicine, Liverpool, UK

Contact address: Joseph Pryce, Department of Clinical Sciences, Liverpool School of Tropical Medicine, Pembroke Place, Liverpool, L3 5QA, UK. joseph.pryce@lstmed.ac.uk.

Editorial group: Cochrane Infectious Diseases Group.
Publication status and date: New, published in Issue 6, 2017.

Citation: Pryce J, Choi L, Malone D. Insecticide space spraying for preventing malaria transmission. *Cochrane Database of Systematic Reviews* 2017, Issue 6. Art. No.: CD012689. DOI: 10.1002/14651858.CD012689.

ABSTRACT

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

Primary objective

To evaluate the impact of space spraying on malaria transmission and vector populations, or the incremental impact when applied in combination with other malaria control methods, in comparison to equivalent conditions with no space spraying intervention.

Secondary objective

To guide future evaluations of strategies for which there is currently insufficient evidence to reliably assess the impact on malaria transmission, by identifying the following.

- The range of space spraying strategies that have been trialled.
- Potentially promising strategies that have been used and warrant further evaluation.
- Strategies that have been used and appear unlikely to warrant further evaluation (for example, because they were found to be infeasible or unacceptable).

BACKGROUND

Description of the condition

WIth one child dying from malaria every two minutes, malaria remains the world's most serious vector-borne disease. In 2015, an estimated 212 million new cases arose globally and the disease caused 429,000 deaths, including 303,000 children under the age of five (WHO 2016a). Most of the malaria burden falls on people living in sub-Saharan Africa, where 90% of the total incidence and 92% of all deaths occur (WHO 2016a). Malaria is also a leading cause of global morbidity and was responsible for between 63 and 110 million disability-adjusted life years (DALYs) in 2010 (Murray 2012).

The *Plasmodium* parasite species that cause malaria are transmitted by the bite of a female *Anopheles* mosquito, and malaria preven-

tion methods are predominantly geared towards reducing human contact with infective mosquitoes. Insecticide-treated nets (ITNs) and indoor residual spraying (IRS) prevent malaria transmission in a variety of settings, and these methods have formed a central component of the global strategy for malaria control (Lengeler 2004; Pluess 2010; WHO 2015). Between 2010 and 2015 the estimated percentage of the at-risk population sleeping under an ITN rose from 30% to 53%. This drive has coincided with a reduction in disease incidence of 21%, while malaria-related deaths have fallen by 29% (WHO 2016a). However, these successes have not been universal. Of the 91 countries with active transmission of malaria, only 40 are on course to achieve the Global Technical Strategy's target of a 40% incidence reduction by 2020 (WHO 2015; WHO 2016a).

Description of the intervention

Space spraying refers to the process of dispersing liquid droplets of insecticide into an area as a fog, with the aim of knocking down and killing adult insects (Figure 1). For the purposes of this Cochrane Review, the term implies distribution of insecticide on a population level, rather than household use.

Figure 1. Space spraying with handheld equipment to control the mosquito population in Thailand

There are two different mechanisms for generating the fog for space spraying. Thermal fogs use hot gas to vaporize a solution of insecticide in a typically oil-based carrier liquid. Upon spraying, the vapour interacts with colder air and forms a dense fog. In contrast, cold fogs are formed without the use of external heat, passing the insecticide mixture instead through a mechanical apparatus such as a high pressure nozzle or high-speed air flow. Cold fogging commonly uses ultra-low-volume (ULV) preparations of insecticide. The insecticide may also be delivered in three different ways; using equipment that is either hand-held, vehicle-mounted, or applied from an aircraft (WHO 2003). Table 1 details the insecticides and doses currently recommended by the World Health Organization (WHO) for space spraying use to control mosquitoes (WHO 2016b).

Space spraying is regularly used in other public health and pest control programmes. The intervention is an often-used strategy for controlling outbreaks of dengue fever, a mosquito-borne viral

disease with endemic regions that overlap extensively with those of malaria (Esu 2010; Epelboin 2012). Both ground and aerial spraying of insecticides have been regularly employed for the control of tsetse flies and for other pests of public health or agricultural importance (WHO 2003; Adam 2013).

Both thermal and cold fog applications are only effective while the droplets remain airborne (WHO 2003). This length of time is mainly dependent on the size of droplets distributed; a 10 μm droplet spray will fall by 10 m in one hour, while 100 μm droplets will fall the same distance in 36 seconds. *Anopheles* mosquitoes typically bite in the evening, at night and in the early morning, and it is recommended that the timing of spraying coincides with this period of peak activity (WHO 2003; Pates 2005). Space spraying is sometimes conducted during the day. In these cases, the intention is to reach and kill mosquitoes in their resting locations, or induce them to take flight through the fog (Najera 2003). Space spraying targets only the current adult mosquito population. The technique has little or no residual activity, and as juvenile stages are not vulnerable to space spraying, multiple applications are required to prevent the adult population being replaced (Najera 2003; Bonds 2012).

How the intervention might work

George Macdonald's theory of vectorial capacity can be used to explain the impact of malaria vector control interventions. Vectorial capacity is a theoretical estimate of the intensity of transmission, equivalent to the basic reproduction ratio of a disease. It describes the total number of potentially infectious bites that would eventually arise from all the mosquitoes in a population biting a single perfectly-infectious human on a single day. The Macdonald model shows that vectorial capacity is highly sensitive to interventions that target the adult mosquito population, as they cause a reduction in both the ratio of mosquitoes to humans and the probability of mosquito survival (Macdonald 1952). If effective, space spraying interventions will therefore have a direct impact on the intensity of transmission. Assuming that the number of infections arising in humans is relative to the number of infectious bites received, this will further lead to a reduction in the number of clinical cases of malaria (Smith 2007).

Why it is important to do this review

ITNs and IRS successfully exploit the anthropophilic (human-biting), endophilic (indoor resting), endophagic (indoor biting), and nocturnal behaviours of Africa's most-efficient malaria vectors, *Anopheles gambiae* and *Anopheles funestus* (Pates 2005; Sinka 2010). In areas of low to moderate transmission, these interventions can be sufficient to reduce parasite prevalence to elimination thresholds, but additional control measures will be required in settings with high transmission or more challenging vector species (Griffin 2010; Chaccour 2016). Space spraying may have a role in reducing transmission in such settings as it will impact equally upon behaviourally-different species. This is of particular interest in the current and future climate as coverage of ITNs increases and transmission via exophagic and zoophagic vector species becomes more important.

The WHO guidelines for judicious insecticide use state that space spraying may be advisable as an emergency response to malaria epidemics, providing resources are available for its immediate application, and that the approach has previously had success against the target species (Najera 2003). This is particularly recommended for densely-populated areas with little potential for IRS, such as camps for refugees and displaced people (WHO 2013; WHO 2015).

However, the use of space spraying for malaria control has been limited. This may be due to the difficulty associated with undertaking space spraying at night, when *Anopheles* mosquitoes are most active, or the view that day-time fogs do not penetrate into the resting sites of *Anopheles* mosquitoes (Najera 2003). Due to a shortage of robust evidence, there remains widespread uncertainty over whether space spraying has any impact on malaria transmission. Despite its use in a variety of epidemic and emergency situations, there is a perception that space spraying is only performed as a public relations exercise (Najera 2003). Space spraying is also expensive to implement on a routine basis as it requires both specialized equipment and trained staff, in addition to large quantities of insecticide.

To achieve a target as ambitious as the eradication of malaria, complete clarity is required regarding the effectiveness of available control methods. Understanding the impact of space spraying will allow the malaria community, including investors, researchers, and disease control strategists, to make informed decisions regarding the allocation of resources and to maximize the benefit of investments.

OBJECTIVES

Primary objective

To evaluate the impact of space spraying on malaria transmission and vector populations, or the incremental impact when applied in combination with other malaria control methods, in comparison to equivalent conditions with no space spraying intervention.

Secondary objective

To guide future evaluations of strategies for which there is currently insufficient evidence to reliably assess the impact on malaria transmission, by identifying the following.

- The range of space spraying strategies that have been trialled.
- Potentially promising strategies that have been used and warrant further evaluation.

- Strategies that have been used and appear unlikely to warrant further evaluation (for example, because they were found to be infeasible or unacceptable).

METHODS

Criteria for considering studies for this review

Types of studies

For our primary objective, we will include the following types of studies.

- Cluster-randomized controlled trials (cRCTs) with:
  - the unit of randomization being a cluster;
  - evidence of baseline equivalence;
  - monitoring of at least one transmission season; and
  - at least two clusters per arm. As the two interventions are distributed at a community level, we do not expect to find trials with individual randomization.
- Interrupted time series (ITS) designs with:
  - a clearly defined point in time when the intervention occurred; and
  - at least three data points before and three after the intervention.
- Randomized cross-over studies with:
  - a clearly defined point in time when the cross-over occurred; and
  - monitoring of at least two transmission seasons before and after the cross-over.
- Controlled before-and-after studies (CBAs) with:
  - a contemporaneous control group;
  - monitoring of at least one transmission season before and after the intervention; and
  - at least two sites per treatment arm.

As part of our secondary objective to review a broader range of space spraying strategies that have been trialled, we will include the following study designs that provide little or no reliable evidence regarding effects.

- CBA studies with only one site per treatment arm.
- ITS studies with monitoring of at least two transmission seasons before and after the intervention.

Types of participants

Children and adults living in malaria transmission settings.

Types of interventions

Intervention

- Interventions that utilise space spraying of insecticides with the purpose of knocking down and killing adult *Anopheles* mosquitoes.
- Interventions may include thermal fogging or cold aerosols distributed through pedestrian (handheld/backpack), ground vehicle, or aerial means.
- Insecticides applied in repetitions, with a minimum of two sprays.

Control

- Equivalent regions that did not receive the above-named space spraying interventions.
- Equivalent regions that received space-spraying with an alternative public health insecticide.
- The control group must not have received any other malaria-co-intervention(s) that differed from the intervention arm.

Types of outcome measures

We will include studies that report any of the following outcomes.

Primary outcomes

- Incidence: measured as a count per person unit time of (a) infections or (b) new infections, following radical cure to avoid measuring pre-existing infections. We define infection as any symptom, including fever, with confirmed parasitaemia (by blood smear microscopy or rapid diagnostic test (RDT)).
- Parasite prevalence: the proportion of surveyed individuals with confirmed parasitaemia.

Secondary outcomes

Epidemiological outcomes

- All-cause mortality.
- Number of people with severe disease: we will use site specific definitions, provided they include (a) and either (b) or (c): (a) demonstration of parasitaemia by blood smear; (b) symptoms of cerebral malaria including coma, prostration, or multiple seizures; (c) severe, life-threatening anaemia.
- Number of people with uncomplicated clinical malaria episodes: we will use site-specific definitions, provided they include (a) demonstration of malaria parasites by either blood smear or RDT, or both, and (b) clinical symptoms including fever detected passively or actively.

Entomological outcomes

- Entomological Inoculation Rate (EIR): the estimated number of bites by infectious mosquitoes per person per unit time. This is measured using the human biting rate (the number of mosquitoes biting an individual over a stated period measured directly using human baits or indirectly using light traps, knock-down catches, baited huts, or other methods of biting rate determination) multiplied by the sporozoite rate.
- Adult mosquito density: measured by a technique previously shown to be appropriate for the vector (measured using human baits, light traps, knock-down catches, baited huts, or other methods).
- Sporozoite rate.

Adverse events

Any indicators of adverse events of the intervention, including the following.

- Reports of poisoning in humans due to increased exposure to insecticide.
- Environmental impacts, such as changes to the biodiversity and ecosystem, due to the addition of insecticides.

Search methods for identification of studies

We will attempt to identify all relevant trials regardless of language or publication status (published, unpublished, in press, and in progress).

Electronic searches

We will search the following databases using the search terms and strategy described in Appendix 1, which we will adapt to each of the specific databases: the Cochrane Infectious Diseases Group Specialized Register; the Central Register of Controlled Trials (CENTRAL), published in the Cochrane Library; MEDLINE (PubMed); Embase (OVID); CAB Abstracts (Web of Science); and LILACS. We will also search the World Health Organization (WHO) International Clinical Trials Registry Platform (http://www.who.int/ictrp/search/en/), ClinicalTrials.gov (https://clinicaltrials.gov/), and the ISRCTN registry (www.isrctn.com/) to identify ongoing trials, using 'mosquito*', "space spraying", "aerosol", and "fogging" as search terms.

Searching other resources

Organizations (and pharmaceutical companies)

We will contact organizations, including the WHO and the Centers for Disease Control and Prevention (CDC), for ongoing and unpublished trials.

Reference lists

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

Data collection and analysis

Selection of studies

Two review authors (JP and LC) will independently screen the titles and abstracts of articles identified by the literature searches for inclusion. They will assess the full-text articles of potentially relevant trials for inclusion using an eligibility form that is based on inclusion criteria. We will compare included trials and resolve any disagreements by discussion and consensus, with arbitration by a third review author (DM) if necessary. We will ensure that multiple publications of the same trial are included only once. We will list excluded studies, together with their reasons for exclusion, in the 'Characteristics of excluded studies' table. We will illustrate the study selection process in a PRISMA diagram.

Data extraction and management

Two review authors (JP and LC) will independently extract information from the included studies using prepiloted, electronic data extraction forms. In case of differences in extracted data, the two review authors will discuss these differences to reach consensus. If unresolved, further discussion will involve the third review author (DM). In case of missing data, we will contact the original study author(s) for clarification.

We will extract data on the following.

- Trial design: type of trial; method of participant selection; adjustment for clustering (for cRCTs); sample size; method of blinding of participants and personnel.
- Participants: trial settings and population characteristics; recruitment rates; withdrawal and loss to follow-up.
- Intervention: description of intervention (active ingredient, dose, formulation, droplet diameter, droplet density, ground or aerial spraying method, ULV or cold fogging, frequency and timing of application, size of treated area, buffer zone between clusters, caged-mosquito outcomes); co-interventions; description of control; duration of follow-up; coverage of intervention and access to co-interventions; compliance of intervention and any co-interventions.
- Outcomes: definition of outcome; diagnostic method or surveillance method; passive or active case detection; number of events; number of participants or unit time; statistical power; unit of analysis; incomplete outcomes/missing data.
- Other:
    - primary and secondary vector(s) species; vector(s) behaviour (nature, stability, adult habitat, peak biting times, exophilic/endophilic, exophagic/endophagic, anthropophilic/

zoophilic); method of mosquito collection(s); phenotypic insecticide resistance (based on WHO definitions if supplementary WHO cylinder assays or CDC bottle bioassays, or both, were performed whilst the trial was running); genotypic insecticide resistance profile (either performed during the trial or if the trial references data from previous studies done on the same local vector population within the previous five years).

- malaria endemicity; eco-epidemiological setting; population proximity and density; *Plasmodium* species.

For dichotomous outcomes, we will extract the number of participants who experience each outcome and the number of participants in each treatment group. For count data outcomes, we will extract the number of outcomes in the treatment and control groups, and the total person time at risk in each group or the rate ratio, and a measure of variance (for example, standard error). For numerical outcomes we will extract the mean and a measure of variance (standard deviation).

For cRCTs we will record the number of clusters randomized; number of clusters analysed; measure of effect (such as risk ratio, odds ratio, or mean difference) with confidence intervals (CI) or standard deviations; number of participants; and the intracluster correlation coefficient (ICC) value. For non-randomized studies (NRS), we will extract adjusted measures of intervention effects that attempt to control for confounding.

Assessment of risk of bias in included studies

Two review authors (JP and LC) will independently assess risk of bias for each included cRCT using the Cochrane 'Risk of bias' tool, and the five additional criteria listed in Section 16.3.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* relating specifically to cluster-randomized trials (Higgins 2011). We will assess the included NRS for risk of bias using the Cochrane Effective Practice and Organization of Practice (EPOC) 'Risk of bias' tool (Cochrane EPOC 2016). We will resolve any discrepancies through discussion or, if necessary, we will consult the third review author (DM). We will classify judgements of risk of bias as either at low, high, or unclear risk of bias, using summary graphs ('Risk of bias' summary and 'Risk of bias' graph) to display results.

Measures of treatment effect

We will compare intervention and control data using risk ratios and rate ratios. We will use adjusted measures of effect to summarize treatment effect from all included NRS. We will present all results with their associated 95% CIs.

Unit of analysis issues

If included cRCTs have not adjusted for clustering in the analysis, we will attempt to adjust data before combining it. We will attempt to adjust the data by multiplying standard errors by the square root of the design effect (Higgins 2011). If the trial does not report the ICC value, then we will estimate the ICC from a similar trial if possible, or by searching external sources for example ICCs. Alternatively, we will not include cRCTs that have not adjusted for clustering in the meta-analysis but will present results in a separate table.

Dealing with missing data

In case of missing data, we will apply available-case analysis, only including data on the known results. The denominator will be the total number of participants who had data recorded for the specific outcome. For outcomes with no missing data, we plan to perform analyses on an intention-to-treat basis. We will include all participants randomized to each group in the analyses and will analyse participants in the group to which they were randomized to.

Assessment of heterogeneity

We will inspect forest plots for overlapping CIs and will assess statistical heterogeneity in each meta-analysis using the I^2 statistic and Chi^2 test values. We will regard heterogeneity as moderate if I^2 statistic values are between 30% to 60%; substantial if they are between 50% to 90%; and considerable if they are between 75% to 100%. We will regard a Chi^2 test statistic with a P value > 0.10 indicative of statistically significant heterogeneity. We will explore clinical and methodological heterogeneity through consideration of the trial populations, methods and interventions, and by visualization of trial results.

Assessment of reporting biases

If there are 10 or more included trials in each meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually, and use formal tests for funnel plot asymmetry (Harbord 2006). If we detect asymmetry in any of these tests or by a visual assessment, we will explore reasons for asymmetry.

Data synthesis

We will analyse data using Review Manager 5 (RevMan 5) (RevMan 2014). We may pool data from RCTs in a meta-analysis. If we judge that included NRS are both reasonably resistant to biases and relatively homogeneous, we may combine data across studies using meta-analysis (Taggart 2001). We will not include NRS in meta-analyses with RCTs. Meta-analyses for cRCTs will use the crude or unadjusted effect estimates, while meta-analyses for NRS will use the adjusted measures of effect, as per Section 13.6.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Reeves 2011).

We will use fixed-effect meta-analysis to combine data if heterogeneity is absent. If considerable heterogeneity is present, we will combine data using random-effects meta-analysis and report an average treatment effect. We will decide whether to use fixed- or random-effects based on the consideration of clinical and methodological heterogeneity between trials, as described previously.
We will assess the certainty of the evidence using the GRADE approach (Guyatt 2011). We will rate the certainty of the evidence for each primary and adverse event outcome, as described by 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.

RCTs start as high certainty evidence but can be downgraded if there are valid reasons within the following five categories: risk of bias, imprecision, inconsistency, indirectness, and publication bias. Studies can also be upgraded if there is a large effect; a dose response effect; and if all plausible residual confounding would reduce a demonstrated effect or would suggest a spurious effect if no effect was observed (Balshem 2011). We will summarize our findings in a 'Summary of findings' table.

Subgroup analysis and investigation of heterogeneity

We plan to perform the following subgroup analyses.

- Seasonality of malaria (perennial transmission/seasonal transmission/outbreak or high-risk settings).
- Spray equipment used: ground sprays, that is using hand-held or vehicle-mounted equipment, or aerial sprays).
- Time of spraying (between 7am and 6.59pm or 7pm and 6.59am).

We will assess differences between subgroups using the Chi² test, with a P value of less than 0.05 indicating statistically significant differences between subgroups.

Sensitivity analysis

We will perform sensitivity analysis on the primary outcome to see the effect of exclusion of trials at high risk of bias (for allocation concealment and incomplete outcome data) on overall results. If the ICC value is estimated, we will undertake sensitivity analyses to investigate the impact of varying the ICC on results from the meta-analysis.

ACKNOWLEDGEMENTS

Joseph Pryce and Leslie Choi are supported by the Effective Health Care Research Consortium. This Consortium and the editorial base of the Cochrane Infectious Diseases Group (CIDG) is funded by UK aid from the UK Government for the benefit of developing countries (Grant: 5242). The views expressed in this review do not necessarily reflect UK government policy.

We are indebted to the mentorship of Professor Paul Garner, CIDG Co-ordinating Editor.

REFERENCES

Additional references

Adam 2013
Adam Y, Cecchi G, Kgori PM, Marcotty T, Mahama CI, Abavana M, et al. The sequential aerosol technique: a major component in an integrated strategy of intervention against riverine tsetse in Ghana. *PLoS Neglected Tropical Diseases* 2013;**7**(3):e2135. [DOI: 10.1371/journal.pntd.0002135]

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. [DOI: 10.1016/j.jclinepi.2010.07.015]

Bonds 2012
Bonds JA. Ultra-low-volume space sprays in mosquito control: a critical review. *Medical and Veterinary Entomology* 2012;**26**(2):121–30. [DOI: 10.1111/j.1365-2915.2011.00992.x]

Chaccour 2016
Chaccour C, Killeen GF. Mind the gap: residual malaria transmission, veterinary endectocides and livestock as targets for malaria vector control. *Malaria Journal* 2016;**15**: 24. [DOI: 10.1186/s12936-015-1063-y]

Cochrane EPOC 2016
Cochrane Effective Practice, Organisation of Care (EPOC). Suggested risk of bias criteria for EPOC reviews. EPOC Resources for review authors. Available at: http://epoc.cochrane.org/epoc-specific-resources-review-authors (accessed 31 May 2017).

Epelboin 2012
Epelboin L, Hanf M, Dussart P, Ouar-Epelboin S, Djossou F, Nacher M, et al. Is dengue and malaria co-infection more

severe than single infections? A retrospective matched-pair study in French Guiana.. *Malaria Journal* 2012;**11**:142. [DOI: 10.1186/1475-2875-11-142]

Esu 2010
Esu E, Lenhart A, Smith L, Horstick O. Effectiveness of peridomestic space spraying with insecticide on dengue transmission; systematic review. *Tropical Medicine & International Health* 2010;**15**(5):619–31. [DOI: 10.1111/j.1365-3156.2010.02489.x]

Griffin 2010
Griffin JT, Hollingsworth TD, Okell LC, Churcher TS, White M, Hinsley W, et al. Reducing Plasmodium falciparum malaria transmission in Africa: a model-based evaluation of intervention strategies. *PLoS Medicine* 2010;**7**(8):e1000324. [DOI: 10.1371/journal.pmed.1000324]

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.

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.

Higgins 2011
Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ (Clinical research ed.)* 2011;**343**:d5928. [DOI: 10.1136/bmj.d5928]

Lengeler 2004
Lengeler C. Insecticide-treated bed nets and curtains for preventing malaria. *Cochrane Database of Systematic Reviews* 2004, Issue 2. [DOI: 10.1002/14651858.CD000363.pub2]

Macdonald 1952
Macdonald G. The analysis of the sporozoite rate. *Tropical Disease Bulletin* 1952;**49**(6):569–86.

Murray 2012
Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;**380**(9859):2197–223. [DOI: 10.1016/S0140-6736(12)61689-4]

Najera 2003
Najera JA, Zaim M, World Health Organization. Decision making criteria and procedures for judicious use of insecticides (WHO Communicable Disease Control, Prevention and Eradication: WHO Pesticide Evaluation Scheme). 2003. http://apps.who.int/iris/bitstream/10665/67365/1/WHO˙CDS˙WHOPES˙2002.5˙Rev.1.pdf. Geneva: World Health Organization, (accessed 31 May 2017).

Pates 2005
Pates H, Curtis C. Mosquito behavior and vector control. *Annual Review of Entomology* 2005;**50**:53–70.

Pluess 2010
Pluess B, Tanser FC, Lengeler C, Sharp BL. Indoor residual spraying for preventing malaria. *Cochrane Database of Systematic Reviews* 2010, Issue 4. [DOI: 10.1002/14651858.CD006657.pub2]

Reeves 2011
Reeves BC, Deeks JJ, Higgins JPT, Wells GA, on behalf of the Cochrane Non-Randomised Studies Methods Group. Chapter 13: Including non-randomized studies. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

RevMan 2014 [Computer program]
Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Sinka 2010
Sinka ME, Bangs MJ, Manguin S, Coetzee M, Mbogo CM, Hemingway J, et al. The dominant Anopheles vectors of human malaria in Africa, Europe and the Middle East: occurrence data, distribution maps and bionomic précis. *Parasites & Vectors* 2010;**3**:117. [DOI: 10.1186/1756-3305-3-117]

Smith 2007
Smith DL, McKenzie FE, Snow RW, Hay SI. Revisiting the basic reproductive number for malaria and its implications for malaria control. *PLoS Biology* 2007;**5**(3):e42. [DOI: 10.1371/journal.pbio.0050042]

Taggart 2001
Taggart DP, D'Amico R, Altman DG. Effect of arterial revascularisation on survival: a systematic review of studies comparing bilateral and single internal mammary arteries. *Lancet* 2001;**358**(9285):870–5.

WHO 2003
World Health Organization. Space spray application of insecticides for vector and public health pest control: A practitioner's guide (Communicable Disease Control, Prevention and Eradication: WHO Pesticide Evaluation Scheme). 2003. http://apps.who.int/iris/bitstream/10665/68057/1/WHO˙CDS˙WHOPES˙GCDPP˙2003.5.pdf. World Health Organization, (accessed 31 May 2017).

WHO 2013
World Health Organization. Malaria control in humanitarian emergencies - An inter-agency field handbook. Second edition. October 2013. http://www.who.int/malaria/publications/atoz/9789241548656/en/. Second Edition. ISBN: 978 92 4 154865 6: World Health Organisation, (accessed 31 May 2017).

WHO 2015
World Health Organization. Global Technical Strategy for Malaria 2016-2030. Available at: http://www.who.int/malaria/areas/global˙technical˙strategy/en/. World Health Organization, (accessed 31 May 2017).

WHO 2016a
World Health Organization. World Malaria Report 2016. Available at http://www.who.int/malaria/publications/world-malaria-report-2016/report/en/. World Health Organization, (accessed 31 May 2017).

WHO 2016b
World Health Organization. WHO recommended insecticides for space spraying against mosquitoes. Updated 5 February 2016. http://www.who.int/whopes/Space˙Spray˙products˙February˙2016.pdf?ua=1 (accessed 31 May 2017).

* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. WHO-recommended insecticides for space spraying against mosquitoes

Compound and formulation	Concentration (g AI/ha)	
	Cold fog	**Thermal fog**
Deltamethrin ULV	0.5 to 1.0	0.5 to 1.0
Deltamethrin EW	1.0	-
Lambda-cyhalothrin EC	1.0 to 2.0	2.0
Malathion EW and ULV	112 to 600	112 to 600
d-d, trans-cyphenothrin EC	3.5 to 4.0	3.5 to 4.0

Abbreviations: EC: emulsifiable concentrate; EW: emulsion, oil in water; ULV: ultra-low volume liquid; AI: active ingredient

APPENDICES

Appendix 1. MEDLINE search strategy

Search set	Search terms
1	Malaria* Title/Abstract , [Mesh]
2	"Insect Vectors"[Mesh] OR vector* ti, ab OR mosquito* or anophel* Title/Abstract
3	1 or 2
4	"Mosquito Control"[Mesh]
5	"Anopheles"[Mesh]
6	3 or 4 or 5
7	((((aerosol*) OR droplet*) OR "cold fog*") OR "thermal fog* ") OR space spray* OR fogging OR misters Title/Abstract
8	"Mist Blower" OR "fumigant canister*" OR "aerial spray*" OR "spray* equipment" OR "ultralow volume" OR "ultralow-volume" OR ULV Title/Abstract
9	"Aerosols"[Mesh]
10	"Fumigation"[Mesh]
11	7 OR 8 OR 9 OR 10
12	6 AND 11

This is the preliminary search strategy for MEDLINE (PubMed). We will be adapt it for other electronic databases. We will report all search strategies in full in the final version of the review.

CONTRIBUTIONS OF AUTHORS

All authors contributed to the design and development of the protocol, and approved the final protocol.

DECLARATIONS OF INTEREST

JP has no known conflicts of interest.

LC has no known conflicts of interest.

DM is employed by the Innovative Vector Control Consortium (IVCC). The title of the review is related to the use of insecticide applications for malaria vector control. The IVCC as an organization has a programme of working with industry on the development of novel insecticides and other vector control tools. IVCC has no current programmes specifically related to the development of space spray insecticides but one project related to their use in a malaria transmission setting.

SOURCES OF SUPPORT

Internal sources

- Liverpool School of Tropical Medicine, UK.

External sources

- Department for International Development, UK.

Grant: 5242

- World Health Organization (WHO), Switzerland.

WHO Global Malaria Programme Agreement for Performance of Work (APW) Grant 2017 (number 709319)