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TABLE OF CONTENTS

| | |
|------------------------------------|----|
| HEADER | 1 |
| ABSTRACT | 1 |
| BACKGROUND | 1 |
| Figure 1. | 3 |
| OBJECTIVES | 4 |
| METHODS | 4 |
| ACKNOWLEDGEMENTS | 8 |
| REFERENCES | 9 |
| APPENDICES | 10 |
| CONTRIBUTIONS OF AUTHORS | 12 |
| DECLARATIONS OF INTEREST | 12 |
| SOURCES OF SUPPORT | 12 |

[Intervention Protocol]

Larvicing to control malaria

Leslie Choi^{1a}, Anne Wilson^{2b}

¹Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, UK. ²Department of Biosciences, Durham University, Durham, UK

^aThese authors contributed equally to this work. ^bThese authors contributed equally to this work

Contact address: Leslie Choi, Department of Clinical Sciences, Liverpool School of Tropical Medicine, Pembroke Place, Liverpool, L3 5QA, UK. leslie.choi@lstmed.ac.uk.

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ABSTRACT

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

To evaluate whether larvicing controls malaria transmission.

BACKGROUND

Description of the condition

Malaria is caused by the *Plasmodium* parasite, which is transmitted by female *Anopheles* mosquitoes. There are five *Plasmodium* species that cause disease in humans; however, the most important species in terms of disease burden are *Plasmodium falciparum*, which is prevalent in sub-Saharan Africa, and *Plasmodium vivax*, which is more common in central Asia and South America. There were an estimated 212 million malaria cases and 429,000 deaths worldwide due to malaria in 2015 ([WHO 2016](#)). Sub-Saharan Africa carries a disproportionately high share of the malaria burden, with 90% of cases and 92% of malaria deaths in 2015 ([WHO 2016](#)). In high transmission areas, children under five years old are highly susceptible to malaria infection, illness, and death, and accounted for 70% of all malaria deaths in 2015 ([WHO 2016](#)). As well as direct effects on health, malaria is a major cause of poverty and underdevelopment in many countries, due to household and health

system costs, absenteeism from school or work, reduced productivity, and premature death ([Chima 2008](#)). Malaria-endemic countries are, on average, poorer by more than five-fold and have lower rates of economic growth than non-malaria endemic countries, with an average growth of per-capita GDP of 0.4% per year versus 2.3% between 1965 and 1990 ([Sachs 2002](#)).

Vector control tools, such as long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS) of insecticide, play a large role in malaria control, alongside diagnosis and effective treatment of malaria cases, and chemoprevention in some population groups. Scale-up of vector control and diagnosis and treatment has averted 663 million clinical cases of malaria between 2000 and 2015 ([Bhatt 2015](#)). However, a high burden of morbidity and mortality still remains and the World Health Organization (WHO) set out ambitious targets in the Global Technical Strategy to eliminate malaria in at least 35 countries by 2030 ([WHO 2016](#)).

Description of the intervention

Larviciding refers to the regular application of microbial or chemical insecticides to water bodies or water containers to kill the aquatic immature forms of the mosquito (the larvae and pupae) ([Tusting 2013](#)).

Mosquitoes lay their eggs in standing water and the eggs develop through a series of life stages (larvae and pupae) into adults. The type of standing water selected by ovipositing females depends on the species in question and can be natural or man-made, temporary or permanent ([Bruce-Chwatt 1985](#)). For example, *Anopheles stephensi* prefers containers such as water tanks, some species prefer brackish habitats (*Anopheles aquasalis* in Latin America), while others prefer rice land habitats (*Anopheles arabiensis*).

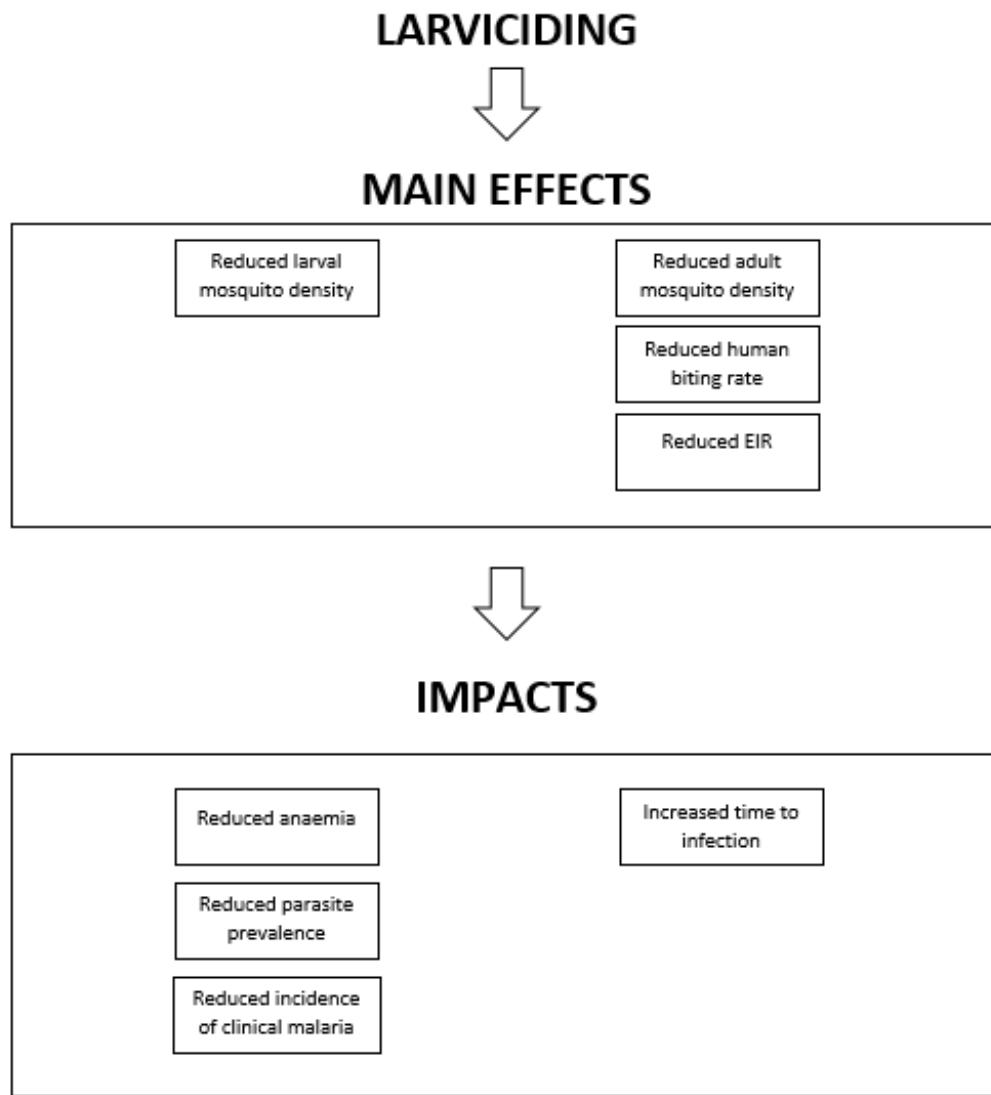
There are a number of different types of larvicide, including insecticides, insect growth regulators, microbial larvicides, and oils. Larvicides have varying modes of action. For example, surface films, such as mineral oils and alcohol-based surface products, suffocate the mosquito larvae and pupae by covering the surface of a water body. This is different from synthetic organic chemicals,

such as organophosphates (the most widely used being temephos) which inhibit cholinesterase and affect the central nervous system of the mosquito. Insect growth regulators (such as pyriproxyfen, methoprene, and diflubenzuron) interfere with insect metamorphosis and prevent adult emergence from the pupal stage. Microbial larvicides (such as *Bacillus thuringiensis israeliensis* (Bti) and *Bacillus sphaericus* (Bs)) function by releasing toxins into the larvae gut which cause the larvae to stop eating and die ([WHO 2013](#)).

How the intervention might work

Larviciding aims to reduce malaria transmission by targeting the immature stages (larvae and pupae) of the anopheline mosquito, to reduce the number of mosquitoes that reach adulthood. By reducing adult vector populations in this fashion, larviciding can reduce the transmission of *Plasmodium* spp. by anopheline mosquitoes, and reduce morbidity and mortality from malaria ([Figure 1](#)).

Figure 1. A logic model that describes the proposed effect of larvicing on various entomological and epidemiological outcomes. Abbreviations: EIR: entomological inoculation rate



Many of the principles behind vector control come from the theory of vectorial capacity developed by George Macdonald in the 1950s ([Macdonald 1957](#)). Vectorial capacity describes the total number of potentially infectious bites that would eventually arise from all the mosquitoes biting a single perfectly infectious (that is, all mosquito bites result in infection) human on a single day. Vectorial capacity can be linked to the basic reproduction ratio of a disease which is the estimated number of secondary infections potentially transmitted by a single infected individual in a totally susceptible population ([Black 1968](#)). The basic reproduction number represents the theoretical estimate of the intensity of transmission. The George-Macdonald model shows that vectorial capacity is most sensitive to changes in adult mosquito survival, which led to the prioritization of IRS and LLINs as vector control tools in the 1950s. However, the vectorial capacity model does not adequately consider the aquatic stages of the vector and so the potential of larviciding is likely to have been underestimated ([Brady 2016](#)). Models show that larval source management (LSM) reduces mosquito population density linearly with coverage if adult mosquitoes avoid laying eggs in treated habitats, but quadratically if eggs are laid in treated habitats and the effort is therefore wasted ([Smith 2013](#)). This would mean that if the most productive habitats are targeted, larviciding could be highly effective even without extensive coverage, unlike previously thought. Larviciding can also operate against both indoor and outdoor (for example, *An. arabiensis*) biting and resting mosquitoes, unlike LLINs and IRS. This is beneficial since in some settings, anthropophilic vectors are able to sustain transmission even with high coverage of LLINs or IRS, or both ([Bayoh 2010](#); [Russell 2010](#); [Lwetoijera 2014](#)), and several studies have also shown evidence of behavioural adaptation of vectors towards early evening biting which can reduce the effectiveness of indoor interventions ([Gatton 2013](#)). Thus larviciding can be effective against 'residual malaria transmission', which is generally defined as transmission that exists despite universal coverage of LLINs or IRS to which vector populations are fully susceptible ([Durnez 2013](#); [Killeen 2014](#)).

Why it is important to do this review

There is a need for new tools in malaria vector control if the goals set by the WHO Global Technical Strategy are to be achieved ([WHO 2016](#)). Malaria vector control currently relies largely on LLINs and IRS. Although the WHO recommends the use of LSM (including larviciding) as a supplementary control measure ([WHO 2013](#)), larviciding is not widely used by malaria control programmes. This is also despite historical success with the use of larviciding for vector control. Paris Green, a arsenic-based compound toxic to larvae, contributed to the elimination of species belonging to the *Anopheles gambiae* complex in Egypt and Brazil ([Soper 1943](#); [Shousha 1948](#)). Larviciding has also been hugely successful against other vector-borne diseases; for example, Bti and

temephos were used to control species of the *Simulium damnosum* complex - vectors of onchocerciasis - in Brazil and the continent of Africa as a supplement to mass drug administration (MDA) ([Sékétéli 2002](#); [Gustavsen 2011](#)).

Larviciding has the potential to overcome several challenges currently facing malaria vector control. Firstly, larviciding is able to target outdoor resting and biting mosquitoes that are less affected by LLINs and IRS. Secondly, it could be used to tackle residual foci of malaria where high coverage of LLINs and IRS is not sufficient to eliminate malaria. Lastly, larviciding could be used in tandem with other interventions as part of an insecticide resistance management strategy. Insecticide resistance has been reported in all major malaria vectors and involves all classes of insecticide (but particularly pyrethroids) and may threaten the effectiveness of insecticide-based vector control ([WHO 2012](#)). The distribution and intensity of insecticide resistance has been increasing over time. Of 73 malaria-endemic countries reporting insecticide resistance monitoring data since 2010, 60 reported resistance to at least one insecticide class and 50 reported resistance to two or more insecticide classes ([WHO 2016](#)). The WHO Global Plan for Insecticide Resistance Management recommends the use of insecticide-based and non-insecticide-based interventions targeting both immature and adult mosquitoes as an insecticide resistance management strategy. This is also aligned with Integrated Vector Management (IVM), an adaptive, evidence-based, and multisectorial approach to vector control, which is recommended by the WHO for more effective, sustainable, and ecologically sound vector control ([WHO 2008](#)).

A Cochrane Review of LSM for controlling malaria already exists, which led to the WHO recommendation on LSM as a supplementary malaria vector control intervention and the publication of a WHO operational manual on LSM ([Tusting 2013](#); [WHO 2013](#)). Although all LSM interventions have the aim of reducing mosquito larvae, the ways they are carried out are very different and effectiveness is likely to differ. For example, habitat modification (a permanent alteration to the environment such as drainage of aquatic habitats) is different to regular application of larvicides to a water body. Due to such differences in different components of LSM, a new assessment of larviciding alone is justified, thus splitting the original Cochrane Review on LSM ([Tusting 2013](#)).

OBJECTIVES

To evaluate whether larviciding controls malaria transmission.

METHODS

Criteria for considering studies for this review

Types of studies

- Randomized controlled trials (RCTs) with: (a) the unit of randomization being a cluster, and (b) at least two clusters per arm. As larvicides are distributed at a community level, we do not expect to find trials with individual randomization.
- Randomized cross over trials with: (a) the unit of randomization being a cluster, (b) at least two clusters per arm, and (c) a suitable washout period during which malaria or entomological indices have returned to baseline levels. As larvicides are distributed at a community level, we do not expect to find trials with individual randomization.
- Controlled before-and-after studies (CBAs) with: (a) a contemporaneous control group, and (b) at least two sites per arm.
- Interrupted time series (ITS) studies with: (a) a clearly defined point in time when the intervention occurred, and (b) at least three data points before and three during or after cessation of larvicide.

We will exclude studies if we observe the following.

- The intervention was applied for less than one year in trials with perennial (year-round) transmission (as reported by the study authors); or less than one transmission season (defined as the period from the onset of rains until one month afterwards) in trials with seasonal transmission (as reported by the study authors).
- The follow-up periods for the intervention and control periods were not identical.

Types of participants

All people living in a rural or urban malarious area that is at any level of endemicity, including both stable and unstable transmission.

We will include studies specific to special groups, such as refugees and soldiers, but we will group and analyse them separately.

Types of interventions

Intervention arm

Larvicide interventions that include insecticides, insect growth regulators, microbial larvicides, or oils. We will exclude plant products, because formulations have not been standardized and studies are thus not comparable. We will also exclude larvivorous fish, since this is a topic of a separate Cochrane Review ([Walshe 2013](#)).

Control

Not receiving larvicide interventions as described above. Any co-interventions such as LLINs, IRS, topical repellents, spatial repellents, environmental manipulation, environmental modification, MDA, and case management must be received in both control and intervention arms.

Types of outcome measures

Studies must report at least one primary outcome for inclusion in the Cochrane Review.

Primary outcomes

- Clinical malaria incidence: we will use site-specific definitions, provided they include: (a) demonstration of malaria parasites by blood smear or a rapid diagnostic test (RDT), or both; and (b) clinical symptoms including fever detected passively or actively.
- Malaria parasitaemia incidence: measured as a count per person unit time of (a) infections or (b) new infections, following treatment to avoid measuring pre-existing infections. Infection is defined as parasitaemia confirmed by blood smear microscopy or RDT.
- Malaria parasite prevalence: the proportion of surveyed individuals with confirmed parasitaemia.

Secondary outcomes

Entomological

- 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 time 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). Adult mosquito density will most likely be reported as bites/person/night for human landing catches and mosquitoes/traps/night for trap catches or pyrethrum spray catches.
- Sporozoite rate.

Epidemiological

- Incidence of severe malaria: 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 or prostration or multiple seizures, or both;
 - (c) severe life-threatening anaemia ([WHO 2015](#)).
- Malaria-related deaths.
- Mean haemoglobin levels (g/dL).
- Anaemia prevalence defined as per WHO cut-offs ([WHO 2011](#)).
- Hospital admissions for malaria.

Adverse events

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

- Non-target effects such as the larvicide killing other animals in the water body.
- Reports of poisoning in humans due to increased exposure to larviciding chemicals.
- Environmental impacts such as changes to the biodiversity and ecosystem due to the addition of larvicides.

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](#): the Cochrane Infectious Diseases Group Specialized Register; the Cochrane Central Register of Controlled Trials (CENTRAL), published in the Cochrane Library; MEDLINE (Pubmed); Embase (OVID); CABS Abstracts (Web of Science); and LILACS (BIREME). We will also search the WHO International Clinical Trials Registry Platform (ICTRP) (<http://www.who.int/ictrp/en/>) and ClinicalTrials.gov (<https://clinicaltrials.gov/ct2/home>) for trials in progress, using “malaria”, “mosquito”, and “larvicide” as search terms.

Searching other resources

We will handsearch the US Armed Forces Pest Management Board Defense Pest Management Literature Retrieval System and the Tropical Diseases Bulletin using the terms: malaria or mosquito and larvicides, from January 2011 to present. [Tusting 2013](#) handsearched these sources up to the end of 2010 and incorporated the results into the Cochrane Review ‘Mosquito larval source management for controlling malaria’.

We will contact researchers in the field to identify unpublished data, and we will check the reference lists of studies identified by the above methods.

Data collection and analysis

Selection of studies

Two review authors (LC and AW) will independently assess the titles and abstracts of trials identified by the literature searches. We will obtain the full-text articles of any potentially relevant articles identified by at least one of the review authors. The same two review authors will assess the full-text articles of potentially relevant studies for inclusion using an eligibility form based on predetermined inclusion criteria. We will resolve any disagreements by discussion and consensus, with arbitration by a third review author if necessary. We will ensure that multiple publications of the same trial are included once. We will list studies excluded after full-text assessment, together with their reasons for exclusion, in a ‘Characteristics of excluded studies’ table. We will illustrate the study selection process in a PRISMA diagram.

Data extraction and management

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

We will extract the following data.

- Trial design: type of trial; method of participant selection; adjustment for clustering (for cluster-RCTs); 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, method, frequency and timing of application, buffer zone between clusters); quality control of the larvicide (for example, WHO Pesticide Evaluation Scheme (WHOPES) approved); quality assurance of implementation of larviciding; co-interventions; description of control; duration of follow-up; passive or active case detection; coverage of larvicide (as reported by the study authors) and co-interventions (for example, vector control, vaccines, chemoprophylaxis, diagnosis and treatment); duration of the activity of the larvicide; compliance (with application of larvicide and co-interventions).
- Outcomes: definition of outcome; diagnostic method or surveillance method; number of events; number of participants or unit time; time point at which outcome was assessed in relation to larviciding implementation, statistical power; unit of analysis; incomplete outcomes or missing data.
- Other:
 - primary and secondary vector(s) species; vector(s) behaviour (nature, stability and extent (number and size) of

aquatic habitats, proximity of aquatic habitats to human habitation, 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, alternatively intensity assays or synergist assays); 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); insecticide and larvicide resistance detected in the larvae (as reported by study authors);

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

For dichotomous outcomes, we will extract the number of participants experiencing each outcome and the number of participants in each treatment group. For count data outcomes, we will extract the number of outcomes in the treatment and control groups, and 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, we will extract the mean and a measure of variance (standard deviation).

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

For non-randomized studies, 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 (LC and AW) will independently assess the risk of bias for each included cluster-RCT 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* that relate specifically to cluster-RCTs (Higgins 2011a; Higgins 2011b). For assessing the risk of bias for randomized cross-over trials, we will use the Cochrane 'Risk of bias' tool also and the additional criteria listed in Section 16.4.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* that relate specifically to randomized cross-over trials (Higgins 2011a). We will assess non-randomized controlled studies and ITS trials for risk of bias using Cochrane Effective Practice and Organisation of Care (EPOC) 'Risk of bias' tool. We will resolve any discrepancies through discussion or by consulting a third review author. We will classify judgements of risk of bias as either at low, high, or unclear risk of bias, and we will use 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 RRs if the outcome is dichotomous. We will present rate data as rate ratios. We will calculate the MD for continuous measures. We will use adjusted measures of effect to summarize treatment effect from non-randomized studies. We will present all results with their associated 95% CIs.

We will report any accounts that signal adverse effects. We appreciate that the specified inclusion criteria are not designed to detect effects on animals in the water, people exposed to the larvicides, and the ecosystem overall, and we will note this in the discussion.

Unit of analysis issues

For cluster-RCTs, we will extract adjusted measures of effect where possible. If the study authors did not perform any adjustment for clustering, we will adjust the raw data using an ICC value. If an ICC value is not reported in the study, we will contact the study authors for this ICC, obtain this from similar studies, or estimate the ICC. We will not present results from cluster-RCTs that are not adjusted for clustering. If we estimate the ICC, we will perform sensitivity analyses to investigate the robustness of our analyses. If we identify studies for inclusion that have multiple intervention arms, we will include data from these studies by either combining treatment arms, or by splitting the control group so that participants are only included in the meta-analysis once (Richardson 2016).

For randomized cross-over trials, we will apply the principles stated in Section 16.4.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* that relate specifically to randomized cross-over trials (Higgins 2011a).

Dealing with missing data

In case of missing data, we will apply available-case analysis and will only include 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.

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 χ^2 test. 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 χ^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.

If there is considerable heterogeneity i.e. an I^2 statistic value of 75% to 100% or inconsistency in the direction of the effect, or both, then we will not perform a meta-analysis.

Assessment of reporting biases

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

Data synthesis

We will analyse data using Review Manager 5 (RevMan 5) (RevMan 2014). We will use a fixed-effect meta-analysis to combine data if heterogeneity is absent. If considerable heterogeneity is present, we will combine data using a random-effects meta-analysis and report an average treatment effect. We will decide whether to use a fixed- or random-effects model based on the consideration of clinical and methodological heterogeneity between trials, as described previously.

We will pool data across follow-up time points for each included study.

Certainty of the evidence

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

Subgroup analysis and investigation of heterogeneity

We will initially analyse all types of larvicide (for example, surface films, synthetic organic chemicals, insect growth regulators, microbial larvicides) together. If there are a sufficient number of studies then we will group these and analyse them separately. We will explore reasons for substantial heterogeneity using subgroup analysis. We plan to perform the following subgroup analyses.

- Seasonality of malaria:
 - perennial, defined as year-round transmission;
 - seasonal (a) as reported by study authors in the manuscript or (b) defined as 75% or more of all malaria episodes occurring in six or less months of the year (Roca-Feltre 2009);
 - epidemic, defined as a sharp rise in malaria incidence, higher than typical levels.
- Extent of aquatic habitat:
 - container habitat;
 - habitats smaller than 1 km² (excluding containers);
 - habitats larger than 1 km.
- Continent:
 - Africa;
 - non-Africa.

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 the overall results. If the ICC value is estimated, we will undertake sensitivity analyses to investigate the impact of varying the ICC value on meta-analysis results.

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* Indicates the major publication for the study

A P P E N D I C E S**Appendix I. Detailed search strategy**

| Search set | CIDG SR ¹ | CENTRAL | MEDLINE | Embase | LILACS | CABS Abstracts |
|------------|----------------------|------------------------|--------------------------|--------------------------|------------|----------------|
| 1 | Mosquito* | Malaria [ti, ab, Mesh] | Malaria [ti, ab, Mesh] | Malaria [ti, ab, Emtree] | Mosquito\$ | Mosquito* |
| 2 | Anopheles | Anopheles [Mesh] | Anopheles [ti, ab, Mesh] | Anopheles ti, ab, Emtree | Anopheles | Anopheles |

(Continued)

| | | | | | | |
|----|-------------|---|--|--|--|---|
| 3 | malaria | Mosquito* ti, ab | Mosquito* ti, ab | Mosquito* ti, ab | malaria | malaria |
| 4 | 1 or 2 or 3 | Mosquito control [Mesh] | Mosquito control [Mesh] | Mosquito control ti, ab | 1 or 2 or 3 | 1 or 2 or 3 |
| 5 | Larvicid* | 1 or 2 or 3 or 4 | 1 or 2 or 3 or 4 | 1 or 2 or 3 or 4 | Larvicid\$ or larval or larva or larvae ti, ab | Larvicid* or larval or larva or larvae ti, ab |
| 6 | 4 and 5 | Larvicid* or larval or larva or larvae ti, ab | Larvicid* or larval or larva or larvae ti, ab | Larvicid* or larval or larva or larvae ti, ab | 4 and 5 | Bacillus thuringiensis |
| 7 | - | "Larval control" ti, ab | "Larval control" ti, ab | "Larval control" ti, ab | - | Bacillus sphericus |
| 8 | - | 6 or 7 | Bacillus thuringiensis [ti, ab, Mesh] | Bacillus thuringiensis ti, ab | - | Paris green |
| 9 | - | 5 and 8 | Bacillus sphericus ti, ab | Bacillus sphericus ti, ab | - | Temefos |
| 10 | - | - | Paris green ti, ab, sn | Paris green ti, ab | - | Pyriproxyfen or methoprene OR fenthion OR abate OR "surface oils" OR "surface films" OR chlorpyrifos OR pirimiphos-methyl OR diflubenzuron OR novaluron OR spinosad |
| 11 | - | - | Temefos ti, ab, sn | Temefos ti, ab | - | Insect growth regulator* |
| 12 | - | - | (Pyriproxyfen or methoprene OR fenthion OR abate OR "surface oils" OR "surface films" OR chlorpyrifos OR pirimiphos-methyl OR diflubenzuron OR novaluron OR spinosad) ti, ab | (Pyriproxyfen or methoprene OR fenthion OR abate OR "surface oils" OR "surface films" OR chlorpyrifos OR pirimiphos-methyl OR diflubenzuron OR novaluron OR spinosad) ti, ab | - | Biological pest control |

(Continued)

| | | | | | | |
|----|---|---|---------------------------------|----------------------------------|---|----------|
| 13 | - | - | Juvenile hormones [Mesh] | Insect growth regulator* ti, ab | - | 5-12/OR |
| 14 | - | - | Insect growth regulator* ti, ab | Biological pest control [Emtree] | - | 4 AND 13 |
| 15 | - | - | Pest Control, Biological [Mesh] | Larvicidal agent [Emtree] | - | - |
| 16 | - | - | 6-15/OR | 6-15/OR | - | - |
| 17 | - | - | 5 AND 16 | 5 AND 16 | - | - |
| 18 | - | - | - | - | - | - |

¹Cochrane Infectious Diseases Group Specialized Register.

CONTRIBUTIONS OF AUTHORS

Both authors contributed equally to this work and approved the final version.

DECLARATIONS OF INTEREST

AW sits on the Innovative Vector Control Consortium (IVCC) External Scientific Advisory Committee 1 (ESAC1), which provides the IVCC management team with independent scientific advice on all projects proposed to the IVCC relating to the development of new products for malaria vector control.

LC has no known conflicts of interest.

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