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Mosquito larval source management for controlling malaria (Protocol)

Thwing J, Fillinger U, Gimnig J, Newman R, Lindsay S

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TABLE OF CONTENTS

HEADER ............................................................................................................. 1
ABSTRACT .......................................................................................................... 1
BACKGROUND .................................................................................................... 2
OBJECTIVES ....................................................................................................... 4
METHODS ........................................................................................................... 4
ACKNOWLEDGEMENTS ...................................................................................... 8
REFERENCES ....................................................................................................... 8
ADDITIONAL TABLES ......................................................................................... 10
APPENDICES ...................................................................................................... 13
HISTORY ............................................................................................................. 15
CONTRIBUTIONS OF AUTHORS ..................................................................... 15
DECLARATIONS OF INTEREST ......................................................................... 15
Mosquito larval source management for controlling malaria

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ABSTRACT

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

To compare mosquito larval source management (excluding biological control with fish) for malaria control with no larval source management, applied either alone or in combination with other malaria control interventions.
**BACKGROUND**

One of the oldest strategies used throughout the world to control malaria is to target the immature stages of the mosquito vectors in their aquatic habitats (Bockarie 1999; Killeen 2002a; Kitron 1989; Walker 2007). This review considers the evidence-base for this strategy.

**Description of the condition**

Malaria, a blood parasite transmitted by anopheline mosquitoes, is the most common vector-borne disease in the world. It remains a major contributor to morbidity and mortality in the developing world, with an estimated 250 million cases and 880,000 deaths each year, the majority in children less than five years old, in sub-Saharan Africa (WHO 2009). While severe disease is seen primarily in children, the impact is felt by the community as a whole, with substantial economic costs. In addition to direct costs of treatment and prevention, indirect costs include lost wages of those caring for the sick, lost productivity, lost potential due to severe malaria or anemia, and decreased investment. The cycle of malaria and poverty is particularly vicious; the poorest are most likely to be affected by malaria, and lose a disproportionate amount of their income to direct and indirect costs of malaria, up to 32% annually (Chima 2008; Teklehaimanot 2008). It is estimated that the economies of countries with endemic malaria grew 1.3% less per year between 1965 and 1990 than other countries (Gallup 2001).

The Global Malaria Action Plan (GMAP) currently advocates four primary strategies to decrease morbidity and mortality due to malaria: population coverage with long-lasting insecticidal nets (LLINs) and indoor residual spraying with insecticide (IRS), prompt effective case management, and intermittent preventive treatment during pregnancy (IPTp) (RBM 2008). Two of these strategies, LLINs and IRS, are vector control strategies and target indoor host-seeking adult mosquitoes. Both LLINs (Lengeler 2004) and IRS (Plass 2010) have been shown to be highly effective in reducing transmission of malaria. Mosquitoes that are the most efficient malaria vectors are also most sensitive to these interventions, as they are late night feeders, anthropophilic (preferring to feed on humans), endophagic (preferring to feed indoors), and endophilic (preferring to rest indoors) (Beatty 1996). However, some malaria vectors are more likely to feed earlier in the evening, or are more likely to feed and rest outdoors, and thus are less likely to be impacted by these interventions. In addition, evidence has been found that mosquitoes can adapt in areas where IRS and LLINs have been widely deployed and, for example, bite earlier in the evening or adapt to living a larger proportion of their lives outdoors (Charlwood 1987; Geissbuhler 2007; Yohannes 2005) as compared to their relatives in areas where these interventions do not achieve high coverage. The development of insecticide resistance is also a looming threat to the sustainability of IRS and LLINs (N’Guessan 2007). Only four classes of insecticides are recommended for IRS and, of these, only one class is recommended for use on nets. Resistance to all four classes of insecticides has been reported from anopheline vectors of malaria (Nauen 2007) and continued reliance on IRS and LLINs is likely to exacerbate the problem.

**Description of the intervention**

Mosquitoes undergo complete metamorphoses and their immature stages develop in stagnant water. While LLINs and IRS target the host-seeking adult mosquitoes, larval source management attempts to decrease malaria transmission by decreasing the number of mosquitoes that reach adulthood. Mosquito larval source management (LSM) is the management of water bodies (aquatic habitats) that are potential breeding sites for mosquitoes in order to prevent the completion of immature development. LSM can be further classified into (1) habitat modification, (2) habitat manipulation, (3) biological control, and (4) larviciding (Rozendaal 1997).

Habitat modification is a permanent change of land and water, including landscaping, drainage of surface water, land reclamation and filling, but also coverage of large water storage containers (wells etc), with mosquito-proof lids and permanent slabs, or complete coverage of water surface with a material that is impenetrable to mosquitoes like expanded polystyrene beads. Habitat manipulation is a recurrent activity, such as water-level manipulation including flushing, drain clearance, shading or exposing habitats to the sun depending on the ecology of the vector. Biological control of mosquitoes means introducing natural enemies into the aquatic habitats, for example predatory fish or invertebrates, parasites or other disease-causing organisms. The most common approach used for malaria control is the introduction of fish in water bodies. This topic will be covered by a separate Cochrane review (Burkot 2009) and will therefore not be included in the analyses here.

Larviciding is the regular application of biological or chemical insecticides to water bodies to control mosquitoes. The available insecticides have different modes of action including (1) surface films like mineral oils and alcohol-based surface products that suffocate larvae and pupae; (2) synthetic organic chemicals such as organophosphates (eg temephos, pirimiphos-methyl) that interfere with the nervous system of the immature larval stages; (3) microbials such as Bacillus thuringiensis israelensis (Bti), and Bacillus sphaericus (Bs) that kill only larvae since their toxins have to be ingested and lead to starvation; and (4) insect-growth regulators such as pyriproxyfen, methoprene and diflubenzuron that interfere with the metamorphoses of the insect and prevent adult emergence from the pupae stage. Historically, Paris Green (copper acetarsenite), an arsenical compound, was extensively used for anopheline larval control (Rozendaal 1997; Shousha 1948; Soper 1943; WHO 2005; WHO 2006).

Mosquito larval source management for controlling malaria (Protocol)

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How the intervention might work

Malaria transmission intensity depends on the density of malaria vectors and the proportion of vector mosquitoes with sporozoites in their salivary glands. The product of these is the entomological inoculation rate (EIR), the number of infected bites received by an individual annually or during a season, and is a measure of transmission intensity. The proportion of the human population with malaria parasites in their blood (parasite prevalence) is linearly related to the log of EIR (Beier 1999).

In general, the larger the mosquito population, the greater will be the potential number of bites by vectors on humans unless people take measures to avoid mosquito bites. As the density of vectors is directly related to the EIR, the greater the mosquito man-biting rate, the greater the malaria transmission, and the higher the incidence of malaria will be. Therefore, if the size of the malaria vector population is limited by interventions that reduce the number of vectors by preventing for example the emergence of adult vectors through larval habitat removal, habitat manipulation, biological control and/or larviciding then transmission of malaria to humans (all other factors remaining the same) will reduce (RBM 2008; Smith 2007). As the density of mosquito vectors of malaria is directly proportional to the EIR, reductions in adult density and biting rates are likely to be very closely related to a decrease in malaria transmission and therefore a decreased number of malaria cases.

Vectorial capacity has been defined as the the efficiency of malaria transmission and this concept was formalized in a mathematical model by (Macdonald 1957). This elegant model demonstrated that malaria transmission was most sensitive to changes in adult survivorship. One implication of this model is that adulticides are more effective in reducing malaria transmission than larvicides. As a result, much of the focus in malaria vector control has been on IRS and ITNs which directly and/or indirectly impact adult survivorship. However, in practice, mosquitoes may avoid insecticides on walls or nets by feeding outdoors or earlier in the night and by resting outdoors where insecticide has not been applied. Furthermore, insecticide resistance, logistical challenges and lack of funds may undermine both ITN and IRS programs. Experience in Africa (Molineaux 1980) as well as other settings (Najera 2001) demonstrated the limits of IRS and indicated the need for additional complementary interventions such as LSM. Anopheline vectors of malaria have a variety of breeding site preferences; some colonize predominately water storage containers (eg Anopheles stephensi), while others use a wide variety of water bodies for their immature development (eg A. gambiae). The abundance of adult mosquitoes is dependent on the number, quality, and sizes of potential habitats, their distance from humans and other blood meal sources, the density of larval stages in the breeding sites, and a number of other environmental factors such as temperature, rainfall patterns, soil types and human behaviour (Gillies 1988; Holstein 1954; Muirhead-Thomson 1951; Rozendaal 1997). Depending on the species, larval habitats can be stable and easily targeted, or dynamic, with new habitats forming after rainfall or due to human activity but disappearing during dry periods. Nevertheless, the mosquito larvae themselves are highly vulnerable to control measures: they are immobile and confined to their aquatic habitat and unlike adults, cannot change their behaviour to avoid control activities targeted at their habitat (Charlwood 1987; Geissbuhler 2007; Yohannes 2005). Therefore, integration of LSM in control programs might accelerate malaria control efforts by targeting an additional life stage either entirely without insecticide or with insecticides that have a different mode of action as compared to those used for adult control. The elimination of breeding sites, where possible, can provide long-term and cost-effective solutions - once a breeding site is gone it does not produce any flying and biting mosquitoes (Castro 2009; Keiser 2005; Utzinger 2001). In many settings large proportions of potential breeding sites for vectors are man-made (Fillinger 2004; Minakawa 2005; Mutuku 2006a; Mwangangi 2007) and could be readily avoided and removed; however, in some instances, this approach may be limited by the domestic and economic function of many habitats (Mutuku 2006a; Utzinger 2001; Utzinger 2002) and larviciding or biological control might be better suited.

Prior to the advent of IRS with DDT, larval control was the primary method of malaria control. The historical literature and more recent reviews indicate that anti-larval mosquito control measures can be a powerful tool against malaria when local conditions are understood well. The Tennessee Valley Authority, which played a key role in the control of malaria in the south-eastern United States, relied primarily on environmental management to reduce mosquito breeding sites (Gartrell 1954), and the Panama Canal was built only through the control of malaria and dengue fever by engineering efforts to eliminate mosquito breeding sites (Dehne 1955). Brazil was able to eliminate A. gambiae by 1940 after its introduction in the late 1920s using the chemical larvicide, Paris Green (Soper 1943; Killeen 2002b). Egypt, which experienced an invasion by A. gambiae in the early 1940s, eliminated it in 1945 using the same strategy (Shousha 1948). LSM has contributed in eradication efforts worldwide (Keiser 2005; Killeen 2002b; Kitron 1989; Russell 1955 Shousha 1948; Soper 1943; Utzinger 2001; Watson 1953).

Recent field evaluations under various eco-epidemiological conditions in Africa showed that larviciding reduced exposure to malaria transmission by 70-92% in areas where breeding sites were well defined and not too extensive (Fillinger 2006; Fillinger 2008; Fillinger 2009), and that the addition of larviciding to LLINs can have a highly significant added benefit in reducing new parasite infections (Fillinger 2009; Geissbuhler 2009).

Why it is important to do this review

Today vector control programs are being encouraged to develop Integrated Vector Management (IVM) (WHO 2008) strategies for the control of malaria and other vector borne diseases. In IVM,
multiple tools are recommended to increase effectiveness and reduce our dependency on insecticides. LSM might have the capacity to supplement the prioritized vector control measures since it will attack not only the indoor vector populations but also those vectors that remain less affected by LLINs and IRS like the outdoor biting and/or resting *A. arabiensis* or secondary vectors which are less anthropophilic and sustain low transmission after high LLIN/IRS coverage. Moreover, the wide diversity in the modes of action of larvicides in combination with environmental modifications and manipulations could represent an opportunity to manage insecticide resistance and to maintain the longevity of existing and widely used active ingredients and offers an important opportunity to reduce the overall dependence on insecticides.

LSM has recently received renewed attention by the international scientific community (*Chen* 2006; *Fillinger* 2003; *Fillinger* 2006; *Fillinger* 2008; *Geissbuhler* 2009; *Gu* 2005; *Keiser* 2005; *Killeen* 2002b; *Mutuku* 2006a; *Shilu* 2007; *Urzinger* 2002; *Walker* 2007; *Yohannes* 2005) and its potential has been demonstrated for contemporary Africa (*Fillinger* 2009; *Geissbuhler* 2009). Ecological and historical evaluations are also leading to a healthy debate on how to operationalize, target and evaluate such approaches (*Fillinger* 2008; *Killeen* 2006; *Mukabana* 2006; *Mutuku* 2006a). As a consequence, LSM has been included in the latest GMAP of the Roll Back Malaria Partnership, though emphasizing that more work is needed before LSM ‘can be considered on par with LLINs and IRS’ (*RB M* 2008). The document outlines that in areas where malaria transmission is low to moderate, and seasonal or focal, the integration of LSM can be appropriate. It is viewed as a targeted approach in addition to LLINs and/or IRS. The added value of LSM is especially anticipated during the phase of ‘sustained control’ (as opposed to ‘scale-up-for-impact’) ‘as the burden goes down and targeted approaches towards breeding sites can be very effective in reducing vector populations’. It is also recognized that its ‘sustainability relies on the ability to conduct continuously reliable surveillance and mapping activities to identify areas where these interventions are most appropriate’. More operational research ‘where larviciding may be feasible’ and more ‘applications where larviciding can be feasible in regions where LSM was previously thought inappropriate’ are encouraged. Moreover, the GMAP defines opportunities to improve vector control interventions in order to achieve malaria elimination. This includes increased emphasis on IVM and LSM. Additional research ‘into applications of larviciding and environmental management in various transmission settings’ is presented as a ‘key opportunity for improving vector control for elimination’ (*RB M* 2008). In the light of these recommendations it is timely to review the evidence-base of the impact of LSM on malaria transmission and parasite infections. LSM needs to be well managed and supervised and requires substantial involvement of local labour. Despite the recent and historical success of LSM, the extent to which it may be applicable in malaria endemic regions is not clear. To justify the investment necessary to integrate LSM strategies in ongoing malaria control efforts sound evidence of the impact of this intervention is required. Although LSM has had some great historical successes, few rigorously evaluated trials exist. We propose to systematically review all reliable data. Even though randomized controlled trials (RCTs) are the most robust study design, such trials with sufficient units (clusters) of replication are very difficult to perform with this type of an environmental intervention (targeting a large surface area of land rather than a person or household or village). Since we expect to find only very few, if any, RCTs, other non-randomized trials will also be considered for analysis.

**OBJECTIVES**

To compare mosquito larval source management (excluding biological control with fish) for malaria control with no larval source management, applied either alone or in combination with other malaria control interventions

**METHODS**

Criteria for considering studies for this review

Types of studies

- Randomized controlled trials for which the unit of randomization is the cluster (eg village). Trials will be excluded if:
  - There are less than two clusters, one in each arm.
  - Ecological, entomological, clinical baseline characteristics and access to antimalaria interventions in intervention and controls are non-comparable in terms of rainfall, vector species, biting habits, and population, types of vector breeding sites, transmission intensity, transmission season, implementation of other malaria control or monitoring interventions.
  - The follow up periods for the intervention and control groups differ.

- Non-randomized controlled trial for which the unit of allocation is the cluster. Trials will be excluded if:
  - There are less than two clusters, one in each arm.
  - Ecological, entomological, clinical baseline characteristics and access to antimalaria interventions in intervention and controls are non-comparable in terms of rainfall, vector species, biting habits, and population, types of vector breeding sites, transmission intensity, transmission season, implementation of other malaria control or monitoring interventions; or baseline characteristics are not reported.
The follow up periods for the intervention and control groups differ.

- **Cross-over time series design** (a study population receives the interventions in sequence and observations are taken at multiple time points). Studies will be excluded if:
  - Interventions other than larvicides, such as habitat modification, which are likely to be more permanent, are compared.
  - There is a washout period less than would be expected for complete disappearance of the larvicide in question, based on reported longevity of the larvicide.

- **Uncontrolled longitudinal study** (observations are made on a series of individuals receiving the same intervention, before and after an intervention but with no control group). Studies will be excluded if:
  - There is not at least one year of baseline data, or in places with strong seasonal transmission, one transmission period (corresponding with onset of rains until one month afterward).
  - Interventions other than larvicides are introduced during the study period.

- **Interrupted time series** (uses observations at multiple time points before and after an intervention.) Studies will be excluded if:
  - There is not at least one year of baseline data, or in places with strong seasonal transmission, one transmission period (corresponding with onset of rains until one month afterward).
  - Interventions other than larvicides are introduced during the study period.

Additionally, studies of any type will be excluded if:

- The intervention is applied for less than a year in trials without strong seasonal transmission; or less than a transmission season (defined as the period from the onset of rains until one month afterward) in trials with strong seasonal transmission.
- None of the types of outcomes of interest in this review are reported.

**Types of participants**
Humans of all ages residing in rural and urban malaria endemic areas.

**Types of interventions**

**Intervention**
- Interventions aiming at reducing the emergence of adult vectors from aquatic habitats, including combinations of the following: habitat modification; habitat manipulation; biological control (excluding larvivorous fish); and larviciding.

- Larvicides will include: surface films like mineral oils and alcohol-based surface products; synthetic organic chemicals such as organochlorines and organophosphates; microbials; insect-growth regulators; and copper acetarsenate (Paris Green).
- Environmental interventions that do not target breeding sites, such as removal of vegetation around homes, will not be considered. Any program that includes larvivorous fish will also be excluded, as this is being covered in a separate Cochrane review, unless both intervention and control areas are equally treated with larvivorous fish as part of a combination of malaria interventions.
- Complete coverage of water surface with a material that is impenetrable to mosquitoes like expanded polystyrene beads will be considered under habitat manipulation.
- Plant products will not be considered as formulations have not been standardized and studies are thus not comparable.

**Control**
- No intervention.

**Additional interventions**
Any additional non-LSM antimalarial interventions must be equally applied to the intervention and control groups.

**Types of outcome measures**

**Primary outcomes**
1. Prevalence of diagnostically confirmed malaria (rapid diagnostic test or microscopy).
2. Incidence of diagnostically confirmed malaria (rapid diagnostic test or microscopy).

**Secondary outcomes**
1. Vector biting rates (measured directly using human baits or indirectly using light traps, knock-down catches or other proxy indicators).
4. Total under five mortality.
5. Time to infection.

**Search methods for identification of studies**
We will attempt to identify all relevant trials regardless of language or publication status (published, unpublished, in press and in progress).
Electronic searches

We will search the following databases using the search terms and strategy described in Appendix 1: Cochrane Infectious Diseases Group Specialized Register; Cochrane Central Register of Controlled Trials (CENTRAL), published in The Cochrane Library; MEDLINE; EMBASE; CABS Abstracts; and LILACS. We will handsearch the Tropical Diseases Bulletin from 1900 to 2010 and the archives of the World Health Organization. We will also search the metaRegister of Controlled Trials (mRCT), and the literature database of the Armed Forces Pest Management Board using the terms: malaria AND mosquito control.

Searching other resources

Reference lists

We will also check the reference lists of all studies identified by the above methods and of previously published reviews.

Conference proceedings

We will search the conference proceedings of the MIM Pan-African Malaria Conferences, the American Society of Tropical Medicine and Hygiene, the American Mosquito Control Association and the Society for Vector Ecology for relevant abstracts.

Researchers and organizations

We will contact heads of malaria control and prominent researchers in countries with active or former programmes using larval control to request access to both published and unpublished manuscripts describing controlled trials.

Data collection and analysis

Selection of studies

The search results will be split amongst the review authors (UF, JT). The authors will screen the search results for potentially relevant studies. JG and SL will retrieve the corresponding full articles and will assess eligibility using an eligibility form. Two authors will independently screen each search result and assess each article. Any discrepancies between the eligibility results of the two review authors will be resolved by discussion with a third co-author. If the eligibility is unclear we will write to the study authors for clarification. The studies’ reports will be scrutinized to ensure that multiple publications from the same study are included only once. We will list the excluded studies and the reasons for their exclusion in ‘Characteristics of Excluded Studies’.

Data extraction and management

UF, JT and SL will extract data from the study reports. Two co-authors will independently extract data from each study report into a pre-designed data extraction form. Any discrepancies between the eligibility results of the two review authors will be resolved by discussion with a third co-author. If relevant data is unclear or not reported we will write to the trial authors for clarification.

Data extraction for cluster randomized studies

For trials randomized using clusters, we will record the number of clusters in the trial, the average size of clusters, and the unit of randomization (eg household or community). The statistical methods used to analyse the trial will be documented if possible and the methods examined for adjustments for clustering or other covariates. When reported, estimates of the intra-cluster correlation (ICC) coefficient for each outcome should be recorded. Authors should be contacted to request missing information. For cluster trials, where results have been adjusted for clustering, the point estimate will be extracted and the 95% confidence interval reported. If the results are not adjusted for clustering, for dichotomous outcomes we will extract the number of participants experiencing the event and the number of participants in each treatment group; for continuous outcomes we will aim to extract arithmetic means and standard deviations for each treatment group together with numbers of participants in each group, geometric means and standard errors or median ranges; and for count data we will extract the number of events in the treatment and control group and the total person time at risk in each group.

Data extraction for non-randomized studies

For non-randomized trials, we will extract the same information as for cluster randomized trials that have not been adjusted for clustering. We will extract details regarding the methods undertaken with regard to the study design. When the studies have adjusted for a covariate in the analyses and reported an adjusted measure of effect, we will extract the measure of effect and its standard error and record the variable(s) for which the analyses were adjusted.

Assessment of risk of bias in included studies

UF and JG will assess the risk of bias for studies. Two co-authors will independently assess the risk of bias for each study using the Effective Practice and Organisation of Care (EPOC) risk of bias assessment form. Any discrepancies between the eligibility results of the review authors will be resolved by discussion with a third co-author. If relevant data are unclear or not reported we will write to the trial authors for clarification. Please see Table 1 for criteria for low, high, and unclear risk of bias for each type of bias risk for each study type. Particular attention will be paid to comparability of baseline characteristics in controlled trials in terms of: seasonality, that the con-
trol site(s) are comparable in relation to malaria endemicity, vector, type of breeding sites, other interventions, and monitoring.

**Measures of treatment effect**
For dichotomous outcomes (infection with malaria), we will present the risk ratio and when continuous outcomes (the entomological outcomes) are summarized by arithmetic means and standard deviations, we will report the mean difference. We will compare geometric means using geometric mean ratios and combine them on a log scale using the generic inverse variance method. All results will be presented with 95% confidence intervals. For count data, we will present rate ratios.

**Unit of analysis issues**
When the analyses have not adjusted for clustering, we will attempt to adjust the results for clustering, by multiplying the standard errors of the estimates by the square root of the design effect where the design effect is calculated as $DEff=1+(m-1)\times ICC$. This requires information to be reported (ie the average cluster size (m) and the intra-cluster correlation coefficient (ICC). If ICC is not available but a design effect is given, or reliably available from a very similar study, we will divide the sample size by the design effect to determine the effective sample size. In this case, for dichotomous data, we will divide both the sample size and the number experiencing the event by the design effect. If this is not available, we will estimate ICC by the following equation: ICC = $\left[\frac{\text{Adjusted SE}/\text{SE}}{\text{SE}^2 - 1}/m - 1.\right]$

**Dealing with missing data**
We will report whether patients, communities/villages have been lost to follow up during the time period of the study; If there is no missing data, we will do an intention to treat analysis; if there is missing data, we will perform a complete case analysis.

**Assessment of heterogeneity**
When cluster randomized trials are combined in meta-analysis, we will inspect the forest plots to detect overlapping confidence intervals, apply the chi-squared test with a P value of 0.10 used to indicate statistical significance, and also implement the I² statistic and P value from a chi$^2$ test. When substantial heterogeneity is determined from the assessments of heterogeneity or when a pooled meta-analysis result is considered to be meaningless because of clinical heterogeneity, we will not carry out meta-analysis but will present a forest plot with the pooled effect suppressed and report the I² statistic and P value from a chi$^2$ test.

**Subgroup analysis and investigation of heterogeneity**
If numerous cluster randomized trials are combined in meta-analysis, subgroup analyses will be used to investigate heterogeneity. Given the potential for impact of larval source management to be different according to ecological setting, if sufficient trials exist, we will perform subgroup analyses according to the following criteria: location (Africa vs other); breeding site (discrete eg pit vs diffuse eg rice field, swamp), type of intervention (larvicide vs habitat manipulation); urban/rural; or transmission intensity (EIR > or <1). Because we expect to find heterogeneity, and that the majority of trials will be non-randomized, we will present the studies included in tables with the following variables: type of intervention, location, breeding site type, primary vectors, transmission intensity, duration of baseline, duration of trial, and baseline comparability. We will present one table per study type.

**Data synthesis**
JT will analyse the data using RevMan 5. The analysis will be stratified by study design i.e cluster randomized trials that adjust for clustering, cluster randomized trials that do not adjust for clustering, cross-over trials, controlled but non-randomized studies, and uncontrolled trials.

**Cluster randomized studies**
If the results of the cluster randomized trials are not adjusted for clustering then the result will be presented in a table since the confidence interval of unadjusted results are artificially narrow and could be misinterpreted in a meta-analysis.

Cluster randomized trials that do adjust for clustering will be combined in meta-analysis. When no statistically significant heterogeneity is detected, the fixed-effect meta-analysis model will be applied; when statistically significant heterogeneity is observed within groups that cannot be explained by subgroup or sensitivity analyses, a random-effects meta-analysis model will be applied to synthesize the data. When substantial heterogeneity is determined from the assessments of heterogeneity or when a pooled meta-analysis result is considered to be meaningless because of clinical heterogeneity, we will not carry out meta-analysis but will present a forest plot with the pooled effect suppressed and report the I² statistic and P value from a chi$^2$ test.

**Non-randomized studies**
Data from non-randomized studies will be presented in tables. If multiple measures of effect are reported that are adjusted for different variables then each will be reported. If trials use similar enough methods that pooling is justified (for example, trials using weekly Bti, with the same surveillance and outcome data), the generic inverse-variance method will be used to pool data.
Sensitivity analysis

If numerous cluster randomized trials are combined in meta-analysis, a sensitivity analysis including only trials with low risk of bias will be used to investigate the robustness of the results.

ACKNOWLEDGEMENTS

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Macdonald 1957

Minakawa 2005

Molineaux 1980

Muirhead-Thomson 1951

Mukabana 2006

Mutuku 2006a

Mwangangi 2007

N’Guessan 2007

Najera 2001

Mosquito larval source management for controlling malaria (Protocol)

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Nauen 2007

Pluess 2010

RBM 2008

RevMan 5

Rozendaal 1997

Russell 1955

Shililu 2007

Shousha 1948

Smith 2007

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Teklehaimanot 2008

Utzinger 2001

Utzinger 2002

Walker 2007

Watson 1953

WHO 2005

WHO 2006

WHO 2008

WHO 2009

Yohannes 2005

* Indicates the major publication for the study
Table 1. Table 1: Assessment of risk of bias

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Risk of bias component</th>
<th>Low</th>
<th>High</th>
<th>Unclear</th>
</tr>
</thead>
<tbody>
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<td>Sequence generation</td>
<td>Random component in the sequence generation process is described</td>
<td>Non-random method is used.</td>
<td>No or unclear information reported.</td>
</tr>
<tr>
<td></td>
<td>Allocation concealment</td>
<td>Patients and investigators could not foresee assignment.</td>
<td>Patients and investigators could foresee assignment.</td>
<td>No or unclear information reported.</td>
</tr>
<tr>
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<td>Blinding</td>
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<td>No or unclear information reported.</td>
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<tr>
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<td>Not all pre-specified outcomes are reported; or additional outcomes reported</td>
<td>No or unclear information reported.</td>
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<td>Recruitment bias</td>
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<td>If baseline characteristics of the study and control areas are reported and similar</td>
<td>if there are differences between control and intervention areas</td>
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<td>If performance or outcomes were measured prior to the intervention, and no important differences were present across study groups or if the analyses account for an imbalance</td>
<td>If important differences were present and not adjusted for in analysis</td>
<td>If no measurements reported</td>
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<td>if not specified in the paper</td>
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<td><strong>Selective outcome reporting</strong></td>
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<td>All pre-specified outcomes are reported (expected or see protocol)</td>
<td>Not all pre-specified outcomes are reported; or additional outcomes reported</td>
<td>No or unclear information reported</td>
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<td><strong>Interrupted time series studies and longitudinal studies</strong></td>
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<td>If there are compelling arguments that the intervention occurred independently of other changes over time and the outcome was not influenced by other confounding variables/historic events during study period. <em>If Events/variables identified, note what they are.</em></td>
<td>If reported that intervention was not independent of other changes in time</td>
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<td>Shape of the intervention effect pre-specified</td>
<td>if point of analysis is the point of intervention OR a rational explanation for the shape of intervention effect was given by the author(s). Where appropriate, this should include an explanation if the point of analysis is NOT the point of intervention</td>
<td>If it is clear that the condition above is not met</td>
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<td>if the intervention itself was likely to affect data collection (for example, any change in source or method of data collection reported)</td>
<td>If reported that intervention itself was unlikely to affect data collection (for example, sources and methods of data collection were the same before and after the intervention)</td>
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## Appendix 1. Search strategies

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*a* Cochrane Infectious Diseases Group Specialized Register

**HISTORY**

Protocol first published: Issue 1, 2011

**CONTRIBUTIONS OF AUTHORS**

Julie Thwing co-ordinated protocol preparation and will be involved with reviewing search results, extracting data, analysing data, and preparing the final report. Ulrike Fillinger has assisted with writing the protocol and will be involved with reviewing search results, extracting data, and writing the final report. John Gimnig assisted with protocol preparation and will assist with article retrieval and eligibility assessment, and will assist with writing of the final report. Robert Newman was involved in the conception and will be involved in the analysis and writing of the final report. Steve Lindsay was involved in the conception, assisted with writing the protocol, and will assist with article retrieval, eligibility assessment, data abstraction, and writing of the final report.

**DECLARATIONS OF INTEREST**

Fillinger, Lindsay, and Gimnig have been the primary investigators and authors of studies that may be selected for review. There are no other interests to disclose.