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Mosquito larval source management for controlling malaria

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Abstract

Background—Malaria is an important cause of illness and death in people living in many parts of the world, especially sub-Saharan Africa. Long-lasting insecticide treated bed nets (LLINs) and indoor residual spraying (IRS) reduce malaria transmission by targeting the adult mosquito vector and are key components of malaria control programmes. However, mosquito numbers may also be reduced by larval source management (LSM), which targets mosquito larvae as they mature in aquatic habitats. This is conducted by permanently or temporarily reducing the availability of larval habitats (habitat modification and habitat manipulation), or by adding substances to standing water that either kill or inhibit the development of larvae (larviciding).

Objectives—To evaluate the effectiveness of mosquito LSM for preventing malaria.

Search methods—We searched the Cochrane Infectious Diseases Group Specialized Register; Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE; EMBASE; CABS Abstracts; and LILACS up to 24 October 2012. We handsearched the Tropical Diseases Bulletin from 1900 to 2010, the archives of the World Health Organization (up to 11 February 2011), and the literature database of the Armed Forces Pest Management Board (up to 2 March 2011). We also contacted colleagues in the field for relevant articles.

Selection criteria—We included cluster randomized controlled trials (cluster-RCTs), controlled before-and-after trials with at least one year of baseline data, and randomized cross-over trials that

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compared LSM with no LSM for malaria control. We excluded trials that evaluated biological control of anopheline mosquitoes with larvivorous fish.

Data collection and analysis—At least two authors assessed each trial for eligibility. We extracted data and at least two authors independently determined the risk of bias in the included studies. We resolved all disagreements through discussion with a third author. We analyzed the data using Review Manager 5 software.

Main results—We included 13 studies; four cluster-RCTs, eight controlled before-and-after trials, and one randomized cross-over trial. The included studies evaluated habitat modification (one study), habitat modification with larviciding (two studies), habitat manipulation (one study), habitat manipulation plus larviciding (two studies), or larviciding alone (seven studies) in a wide variety of habitats and countries.

Malaria incidence: In two cluster-RCTs undertaken in Sri Lanka, larviciding of abandoned mines, streams, irrigation ditches, and rice paddies reduced malaria incidence by around three-quarters compared to the control (RR 0.26, 95% CI 0.22 to 0.31, 20,124 participants, two trials, *moderate quality evidence*). In three controlled before-and-after trials in urban and rural India and rural Kenya, results were inconsistent (98,233 participants, three trials, *very low quality evidence*). In one trial in urban India, the removal of domestic water containers together with weekly larviciding of canals and stagnant pools reduced malaria incidence by three quarters. In one trial in rural India and one trial in rural Kenya, malaria incidence was higher at baseline in intervention areas than in controls. However dam construction in India, and larviciding of streams and swamps in Kenya, reduced malaria incidence to levels similar to the control areas. In one additional randomized cross-over trial in the flood plains of the Gambia River, where larval habitats were extensive and ill-defined, larviciding by ground teams did not result in a statistically significant reduction in malaria incidence (2039 participants, one trial).

Parasite prevalence: In one cluster-RCT from Sri Lanka, larviciding reduced parasite prevalence by almost 90% (RR 0.11, 95% CI 0.05 to 0.22, 2963 participants, one trial, *moderate quality evidence*). In five controlled before-and-after trials in Greece, India, the Philippines, and Tanzania, LSM resulted in an average reduction in parasite prevalence of around two-thirds (RR 0.32, 95% CI 0.19 to 0.55, 8041 participants, five trials, *moderate quality evidence*). The interventions in these five trials included dam construction to reduce larval habitats, flushing of streams, removal of domestic water containers, and larviciding. In the randomized cross-over trial in the flood plains of the Gambia River, larviciding by ground teams did not significantly reduce parasite prevalence (2039 participants, one trial).

Authors' conclusions—In Africa and Asia, LSM is another policy option, alongside LLINs and IRS, for reducing malaria morbidity in both urban and rural areas where a sufficient proportion of larval habitats can be targeted. Further research is needed to evaluate whether LSM is appropriate or feasible in parts of rural Africa where larval habitats are more extensive.

BACKGROUND

Description of the condition

Malaria is the most common vector-borne disease in the world, caused by *Plasmodium* spp. parasites which are transmitted by adult anopheline mosquitoes. In 2010, the number of

deaths due to malaria was estimated to be between 655,000 (WHO 2011) and 1.24 million (Murray 2012). Most deaths occur in children aged less than five years old in sub-Saharan Africa (WHO 2011). Malaria is both a disease of poverty (Chima 2008; Teklehaimanot 2008), and an impediment to socioeconomic development (Gallup 2001). Acute malaria episodes and chronic disease reduce labour productivity, increase absenteeism from work, and cause premature mortality. At the macroeconomic level, there are broader costs stemming from the effect of malaria on tourism, trade, and foreign investment. The total cost to sub-Saharan Africa has been estimated at around US$12 billion annually (approximately 5.8% of the total sub-Saharan Africa gross domestic product) (Sachs 2001).

The Global Malaria Action Plan (GMAP) currently advocates four primary strategies to decrease malaria morbidity and mortality: 1) population coverage with long-lasting insecticidal nets (LLINs), 2) indoor residual spraying (IRS), 3) prompt effective case management, and 4) intermittent preventive treatment during pregnancy (IPTp) (RBM 2008). Two of these strategies, LLINs and IRS, are methods of vector control that are highly effective in reducing malaria transmission by indoor host-seeking mosquitoes (Lengeler 2004; Pluess 2010).

Description of the intervention

Mosquito larval source management (LSM) is the management of water bodies that are potential larval habitats to prevent the development of immature mosquitoes into adults (Kitron 1989; Bockarie 1999; Killeen 2002a; Walker 2007; Fillinger and Lindsay 2011).

Mosquitoes undergo complete metamorphosis and their immature stages develop in standing water in a range of different habitats. Some anopheline species breed predominately in water storage containers (for example, *Anopheles stephensi*), while other species breed in a wide variety of water bodies (for example, *An. gambiae*). The abundance of adult mosquitoes is dependent on: the number, quality, and size of potential habitats; their distance from humans and other blood meal sources; the density of larval stages in the habitats; and various other environmental factors such as temperature, rainfall patterns, soil types, and human behaviour (Muirhead-Thomson 1951; Holstein 1954; Gillies 1988; Rozendaal 1997). Depending on the vector species, the ecoepidemiological setting, and climatic conditions, mosquito larval habitats can be either stable or dynamic (with new habitats forming after rainfall or due to human activity, but disappearing during dry periods).

LSM can be classified as: (1) habitat modification; (2) habitat manipulation; (3) biological control; or (4) larviciding (Rozendaal 1997). (1) Habitat modification is a permanent change of land and water. It includes landscaping; drainage of surface water; land reclamation and filling; and coverage of large water storage containers (for example, wells) with mosquito-proof lids and permanent slabs, or complete coverage of water surfaces with a material that is impenetrable to mosquitoes (for example, expanded polystyrene beads). (2) Habitat manipulation is a recurrent activity and includes water-level manipulation, flushing of streams, drain clearance, shading, or exposing habitats to the sun depending on the ecology of the vector. (3) Biological control of mosquitoes is the introduction of natural enemies of mosquitoes into 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 larvivorous fish (fish that eat mosquito larvae and pupae) into larval habitats. This topic will be covered by a separate Cochrane review (Burkot 2009). (4) Larviciding is the regular application of biological or chemical insecticides to larval habitats to control mosquitoes. Currently available insecticides have different modes of action. They include surface films such as mineral oils and alcohol-based surface products that suffocate larvae and pupae; synthetic organic chemicals such as organophosphates (for example, temephos and pirimiphos-methyl) that interfere with the nervous system of larvae; microbials such as *Bacillus thuringiensis israeliensis* (*Bti*) and *Bacillus sphaericus* (*Bs*) that kill only larvae since their toxins have to be ingested and lead to starvation; and insect-growth regulators (such as pyriproxyfen, methoprene and diflubenzuron) that interfere with insect metamorphoses and prevent adult emergence from the pupae stage. Historically, Paris Green (copper acetoarsenite), an arsenic-based compound that is toxic to larvae, was extensively used for anopheline larval control (Soper 1943; Shousha 1948; Rozendaal 1997; WHO 2005; WHO 2006a).

How the intervention might work

LSM 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. In this way, LSM may reduce transmission of *Plasmodium* spp. parasites by adult mosquitoes and reduce malaria prevalence and morbidity (Figure 1).

Malaria transmission intensity is determined by the frequency with which malaria vectors bite humans (the human biting rate) and the proportion of vector mosquitoes with sporozoites in their salivary glands (the sporozoite rate). The product of these values is the entomological inoculation rate (EIR), which is the number of infectious bites received by an individual annually or seasonally. In general, the larger the mosquito population, the higher the human biting rate (unless protective measures against mosquito bites are in place) and the higher the EIR. The proportion of the human population with malaria parasites in their blood (parasite prevalence) is related linearly to the log value of the EIR. Parasite prevalence is unlikely to fall unless the EIR is less than one infectious bite per person per year (Beier 1999, Smith 2005). The relationship between EIR and the incidence of clinical malaria is mediated by reduced transmission efficiency at high levels of transmission intensity (Smith 2010), with incidence increasing with EIR before peaking at moderate transmission levels (Ghani 2009). Use of interventions that reduce adult vector populations will reduce the EIR (assuming that all other factors remain the same) (Smith 2007).

Vectorial capacity represents the efficiency of the malaria vector (the expected number of humans infected per day per infected human, assuming perfect transmission efficiency). This concept was formalized mathematically in the Ross-MacDonald model (Macdonald 1957; Smith 2004; Smith 2007), which demonstrated that reducing the daily survival rate of adult mosquitoes produces the greatest reductions in transmission. As a result, malaria vector control has largely focused on the use of IRS and LLINs, which reduce adult survivorship. However, the Ross-Macdonald model does not explicitly consider larval populations (Smith 2013). In practice, mosquitoes may avoid insecticides on walls or nets by feeding outdoors, or earlier in the night, and by resting outdoors (Molineaux 1980; Najera

2001). Only a small proportion of the vector population may be exposed to a fatal dose of insecticide, whilst the majority of the vector population remains unaffected. LSM targets both indoor and outdoor vectors (for example, *An. arabiensis*) and less anthropophilic secondary vectors that sustain transmission despite high coverage using LLIN, or IRS, or both. Mosquito larvae are highly susceptible to vector control measures because they are confined to their aquatic habitat and, unlike adults, cannot develop behavioural resistance to avoid interventions (Charlwood 1987; Yohannes 2005; Geissbühler 2007). LSM might aid malaria control by targeting immature mosquitoes either without insecticide or using insecticides that have a different mode of action than those used for adult control. The elimination of larval habitats (through habitat modification) can provide long-term and cost-effective solutions because once a larval habitat is removed it cannot produce any flying and biting mosquitoes (Utzinger 2001; Keiser 2005; Castro 2009). In many settings, a large proportion of potential larval habitats are man-made (Fillinger 2004; Minakawa 2005; Mutuku 2006a; Mwangangi 2007) and could be readily removed. Where habitats have a domestic or economic function (Utzinger 2001; Utzinger 2002; Mutuku 2006a), larviciding or biological control might be appropriate.

Why it is important to do this review

Prior to the advent of IRS with the insecticide dichlorodiphenyltrichloroethane (DDT), LSM was the primary method of malaria control. 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 larval habitats (Gartrell 1954) and the construction of the Panama Canal was made possible through malaria and dengue fever control by engineering that eliminated mosquito larval habitats (Dehne 1955). Brazil eliminated *An. gambiae* by 1940, following its introduction in the late 1920s, using the chemical larvicide Paris Green (Soper 1943; Killeen 2002b). Egypt eliminated *An. gambiae* in 1945 using the same strategy, following its introduction in the early 1940s (Shousha 1948). LSM has since contributed to elimination efforts elsewhere (Soper 1943; Shousha 1948; Watson 1953; Russell 1955; Kitron 1989; Utzinger 2001; Killeen 2002b; Keiser 2005).

Today, vector control programmes are being encouraged to adopt Integrated Vector Management (IVM) strategies for the control of malaria and other vector borne diseases. In IVM, multiple tools are recommended to increase the efficacy and cost-effectiveness of control efforts and to reduce dependence on insecticides (WHO 2008). LSM might have the capacity to supplement primary vector control measures (LLINs and IRS) since it targets outdoor biting and resting vectors and less anthropophilic vectors that sustain transmission, despite high coverage of LLINs, or IRS, or both. Resistance to all four classes of insecticides available for IRS (of which only one can be used on LLINs), and evidence of behavioural resistance (such as earlier evening biting) in areas with high IRS and LLIN coverage (Yohannes 2005; Geissbühler 2007; Bayoh 2010; Govella 2010) may undermine LLIN and IRS programmes. Continued reliance on these interventions may exacerbate the problem (N'Guessan 2007; Ranson 2011). Complementary methods of vector control, such as LSM, may therefore be increasingly necessary.

Currently, a number of malaria-endemic countries in sub-Saharan Africa and elsewhere are running or planning LSM programmes (Killeen 2002b; Utzinger 2002; Fillinger 2003; Gu 2005; Keiser 2005; Yohannes 2005; Chen 2006; Fillinger 2006; Mutuku 2006a; Shililu 2007; Walker 2007; Fillinger 2008; Geissbühler 2009). However, there is a lack of consensus on how effectively LSM reduces clinical and entomological outcomes. This is partly because few rigorously evaluated studies exist because cluster-RCTs (cRCTs) with sufficient clusters are difficult to perform with this type of environmental intervention. Since the impact of LSM may be mediated by environmental factors, such as the vector species and type of larval habitats, there has also been debate over where and when LSM might be appropriate (Fillinger and Lindsay 2011). Discussions have also focused on how LSM can be operationalized and evaluated because some types of LSM, such as larviciding, need to be well managed, supervised, and require substantial involvement of local labour, similar to the organization of IRS programmes (Killeen 2006; Mukabana 2006; Mutuku 2006a; Fillinger 2008).

The GMAP states that in areas where malaria transmission is low to moderate, and seasonal or focal, targeted LSM may be appropriate in addition to LLINs, or IRS, or both. However, the plan encourages more operational research into LSM application in various settings (RBM 2008). More recently, the World Health Organization (WHO) published a position statement on the role of larviciding for malaria control in sub-Saharan Africa, giving interim recommendations whilst urging caution due to gaps in the evidence (WHO 2012). Given the lack of consensus on the role of LSM in malaria control, it is timely to review the evidence for its impact on clinical and entomological outcomes, and to identify in which settings and under what conditions LSM is appropriate.

OBJECTIVES

To compare mosquito LSM (excluding biological control with larvivorous fish) for malaria control, applied either alone or in combination with other malaria control interventions, with no LSM.

METHODS

Criteria for considering studies for this review

Types of studies—We included:

- RCTs for which the unit of randomization was the cluster, provided that:
  - Intervention and control groups were comparable in terms of ecological baseline characteristics and access to antimalarial interventions, including rainfall, vector species, biting habits, and population, types of vector larval habitats, transmission intensity, transmission season, implementation of other malaria control or monitoring interventions. We did not include the study if characteristics were not reported.
- Controlled before-and-after trials for which the unit of allocation was the cluster, provided that:

- Intervention and control groups were comparable in terms of ecological baseline characteristics and access to antimalarial interventions, including rainfall, vector species, biting habits, and population, types of vector larval habitats, transmission intensity, transmission season, implementation of other malaria control or monitoring interventions. We did not include the study if characteristics were not reported.
- In non-randomized trials, there was at least one year or one transmission season of baseline data to demonstrate comparability.

- Randomized cross-over trials for which the unit of randomization was the cluster, provided that:
  - The intervention was restricted to larviciding only. We excluded the study if the intervention included habitat modification or manipulation, which are likely to be more permanent.
  - There was a washout period at least as long as that expected for complete disappearance of the larvicide in question, based on reported longevity of the larvicide, and for larval and adult densities to return to normal.

We excluded studies if:

- 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).
- None of the outcomes of interest specified in this review were reported.
- The follow-up periods for the intervention and control periods were not identical.

Types of participants—Children and adults living in rural and urban malaria-endemic areas.

Types of interventions

Intervention: We included interventions that aimed to reduce the emergence of adult vectors from aquatic habitats, including combinations of the following methods:

- Habitat modification: a permanent change of land and water including landscaping; drainage of surface water; land reclamation and filling; and coverage of large water storage containers (for example, wells) with mosquito-proof lids and permanent slabs, or complete coverage of water surfaces with a material that is impenetrable to mosquitoes (such as expanded polystyrene beads).
- Habitat manipulation: a recurrent activity, such as water-level manipulation, flushing, drain clearance, shading, or exposing habitats to the sun depending on the ecology of the vector.
- Larviciding: the regular application of biological or chemical insecticides to water bodies to control mosquitoes, for example surface films such as mineral oils and

alcohol-based surface products; synthetic organic chemicals such as organochlorines and organophosphates; microbials; insectgrowth regulators; and copper acetoarsenite (Paris Green).

- Biological control (excluding larvivorous fish): the introduction of natural enemies into aquatic habitats, for example predatory invertebrates, parasites or other diseasecausing organisms.

We excluded the following interventions:

- Plant products, because formulations have not been standardized and studies are thus not comparable.
- Larvivorous fish, as this is being covered in a separate Cochrane review (Burkot 2009), unless both intervention and control areas were equally treated with larvivorous fish as part of a combination of malaria interventions.
- Interventions that did not target larval habitats, such as removal of vegetation around homes.

Control: No LSM intervention.

Additional interventions (co-interventions): We included studies that described more than one intervention, in which LSM was used in combination with another intervention, providing that the additional interventions were comparable across groups.

Types of outcome measures

Primary outcomes

1. Incidence of malaria: diagnostically confirmed by rapid diagnostic test or microscopy.
2. Parasite prevalence: diagnostically confirmed by rapid diagnostic test or microscopy.

Secondary outcomes

1. Splenomegaly prevalence in children.
2. Anaemia prevalence in children.
3. Time to infection.
4. Total mortality of children aged under five years.
5. EIR: the estimated number of bites by infectious mosquitoes per person per unit time (measured directly using human baits or indirectly using light traps, knock-down catches, baited huts, or other methods of biting rate determination).
6. Adult mosquito density: measured by a technique previously shown to be appropriate for the vector:

i) Human biting rate: number of mosquitoes per person per time period, measured directly using human baits, or indirectly using light traps, knock-down catches, baited huts, or other methods of biting rate determination.

ii) Density measures other than human biting rate: number of mosquitoes per person or catch, measured using light traps, knock-down catches, baited huts, or other methods of adult vector density determination.

Search methods for identification of studies

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

Electronic searches—We searched 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 (May 10, 2013). We handsearched the US Armed Forces Pest Management Board Defense Pest Management Literature Retrieval System (search completed March 2, 2011) and the Tropical Diseases Bulletin from 1900 to 2010 (search completed March 2, 2011) using the terms: malaria AND mosquito control.

Searching other resources

Organizations: We handsearched the archives of the WHO using the terms: malaria AND mosquito control. These archives included WHO Technical Documents pre c1983; the catalogue of the material of the WHO (stored in WHO archives in microform) from 1946 to 1950 and 1950 to 1955; the catalogue of the material of the WHO (stored as centralized files) pre 1991; and the archives of the Parasitology Collection of the Communicable Diseases Documentation Centre at the WHO Headquarters from 1911 to date (search completed February 11, 2011).

Researchers: We contacted heads of malaria control and prominent researchers in countries with active or former programmes using LSM and requested access to both published and unpublished manuscripts describing controlled trials. We made these requests between July 8, 2011 and December 16, 2011.

Data collection and analysis

Selection of studies: SL and JT independently screened the electronic search results for potentially relevant studies. We attempted to retrieve the full articles for all studies identified by either SL or JT. Both LT and JT independently screened the handsearch results for potentially relevant studies. JT, LT, and KB assessed eligibility using an eligibility form. Two authors (JT, LT, or KB) assessed each article independently, and we resolved any disagreements through discussions with the third author. If any disagreement remained, SL or JG made a final judgment. Native speakers evaluated the foreign language studies in consultation with one of the authors. We checked study reports to ensure that multiple

publications from the same study were included only once. We listed excluded studies and the reasons for their exclusion in the ‘Characteristics of excluded studies’ section.

Data extraction and management: LT and KB independently extracted data from the study reports into a pre-designed data extraction form. LT and KB resolved any disagreement through discussion with each another and then with JT. JT reviewed all data extraction. We attempted to collect unreported data by directly contacting study authors. Where results were reported for multiple time points or for multiple areas, we extracted each result and synthesized the data as outlined in the ’Data synthesis’ section.

Data extraction for cluster-RCTs: For trials randomized using clusters, we extracted the number of clusters in the trial, the average size of clusters, and the unit of randomization (for example, household or community). Where possible, we documented the statistical methods used to analyze the trial. We examined the methods for adjustments for clustering or other covariates. We recorded estimates of the intra-cluster correlation (ICC) coefficient for each outcome when they were reported. We contacted authors to request missing information. Where results were not adjusted for clustering, for count data (incidence of clinical malaria) we extracted the number of events in the treatment and control group and the total person time at risk in each group. For dichotomous outcomes (parasite or splenomegaly prevalence), we extracted the number of participants that experienced the event and the number of participants in each treatment group. For continuous outcomes (the entomological outcomes), we extracted arithmetic or geometric means, standard deviations or standard errors, and the number of participants in each treatment group.

Data extraction for controlled before-and-after trials: For controlled before-and-after trials, we extracted the same information as for cluster-RCTs that had not been adjusted for clustering. We extracted details regarding the study design methods. When studies adjusted for covariates in the analyses and reported an adjusted measure of effect, we extracted the measure of effect and its standard error. We recorded the variable or variables used for adjustment.

Data extraction for randomized cross-over trials: For randomized cross-over trials, we extracted the same information as for controlled before-and-after trials.

Assessment of risk of bias in included studies: JT and JG independently assessed the risk of bias for each selected study using the Effective Practice and Organisation of Care (EPOC) risk of bias assessment form (Cochrane 2009). We modified this form to encompass the needs of our study designs. We resolved any discrepancies between the two assessments through discussion with a third co-author. We assigned a judgement of unclear, high, or low risk of bias for each component of each study, as outlined in Table 1. We presented the results in a risk of bias summary and figure.

Measures of treatment effect: For count data (malaria incidence), we presented rate ratios. For dichotomous outcomes (parasite or splenomegaly prevalence), we presented the risk ratio. We summarized continuous outcomes by arithmetic mean values and we reported the percent reduction. We presented all results with 95% CIs.

Unit of analysis issues: When the analyses did not adjust for clustering, we contacted trial authors to ask for estimates of ICC. When these were unavailable, we conducted a sensitivity analysis imputing a range of values (from 0.01 to 0.1) for the ICC. For rate and prevalence estimates, we multiplied the standard errors of the estimates (from an analysis ignoring clustering) by the square root of the design effect, where the design effect was calculated as DEff = 1 + (m - 1)*ICC and m = the average cluster size.

Dealing with missing data: Due to the nature of the study designs, trials did not follow-up individual patients and we do not know the number of missing patients. We extracted data as reported in the studies.

Data synthesis: We calculated the outcome measure (for example, parasite prevalence) separately for each year, month, or survey and we took an unweighted average to aggregate data from multiple years, months, surveys, or sites. We compared data from the follow-up period (for both control and intervention areas) for the same portion of the year to take into account seasonality where baseline data were available only for portion of a year. For data collected from multiple cross-sectional surveys, we used data during or immediately after a transmission season, rather than during a dry season or at the beginning of a transmission season. Where longitudinal data were presented separately for the transmission and non-transmission season, we used the data for the transmission season. For studies where no events were observed in one or both arms, we added a fixed value (0.5) to all cells of study results tables.

Clinical data: For cluster-RCTs and controlled before-and-after trials, we stratified the data by intervention: (1) habitat modification alone; (2) habitat modification with larviciding; (3) habitat manipulation alone; (4) habitat manipulation with larviciding; (5) larviciding alone; or (6) any LSM. We then stratified by outcome: (1) incidence of malaria; (2) parasite prevalence; or (3) splenomegaly prevalence. Finally, we stratified the data by study design: (1) cluster-RCTs; or (2) controlled before-and-after trials. Although the interventions used in these trials were highly variable, we justified pooling of data across interventions in the final analysis as all trials shared the common aim to reduce mosquito numbers. In this respect, we judged the interventions as appropriately different as they were designed to suit the local vector biology and larval habitats.

We presented the data as forest plots. We used fixed effect meta- analysis where we did not detect significant heterogeneity, and random-effects meta-analysis where we found significant heterogeneity. We conducted the analyses using Review Manager (RevMan). For randomized cross-over trials, where each cluster acted as its own control and there were no baseline data, we presented the data in tables. For count data, we calculated rate ratios for each zone so we could compare control and treatment years. For dichotomous outcomes, we calculated risk ratios for each zone so we could compare control and treatment years.

Entomological data: We could not analyze the entomological data using the same methods as for the clinical data because we did not identify a sufficient number of trials. For cluster-RCTs and controlled before-and-after trials, we presented the data in tables. We presented one table for each outcome: (1) EIR; (2) adult mosquito density (human biting rate); and (3)

adult mosquito density (measures other than human biting rate). Within each table, we stratified the data by intervention and then by study design. We presented data from non-randomized cross-over trials in a separate table.

For all studies in which data were available at baseline and post-intervention for at least one control and one intervention site, we adopted a 'difference in differences' (or ratio of ratios for a multi-plicative model) approach to estimate the percent reduction in the outcome due to the intervention. We estimated the effect of the intervention (RR) by using the formula (q1/q0)/(p1/p0), where q1 and q0 are, respectively, the entomological indicators (EIR, mean density, or biting rate) observed in the intervention and control areas post-intervention respectively and p1 and p0 are the corresponding baseline estimates of these entomological indicators. We calculated the percentage reduction in entomological indicators as 100 × (1 - RR). We calculated the 95% CIs for log(RR) using the delta method. We then back-transformed these intervals (we took the anti-log of the lower and upper bounds) to obtain CIs for RR. The difference in differences estimate assumes that: 1) changes over time are similar for the control and intervention sites; and 2) time and intervention effects combine multiplicatively. Estimates will be biased if there is a change that is unrelated to the intervention that does not occur equally across both areas. Estimates would be more robust if they were based on data from multiple control and intervention sites and analysed as in a cluster-RCT (such as, accounting for correlated outcomes in the same cluster).

For studies in which data were only available post-intervention for one control and one intervention site, we calculated the percent reduction in the outcome in the treatment group, as compared to the control group, by the formula 100×(1-(q1/q0)). We did not calculate the 95% CIs.

Where data were available from multiple control or intervention sites, we took the average values of the outcome measures (EIR, mean density, or biting rate) and we gave equal weight to all sites. We averaged the data from multiple time points within a year or transmission season, either pre- or post-intervention, in a similar manner.

Sensitivity analysis: Where we combined numerous trials in meta-analysis, we planned to conduct a sensitivity analysis including only trials with low risk of bias to investigate the robustness of the results. However, since all included studies were at variable risk of bias, we had an insufficient number of trials at low risk of bias and therefore we did not conduct this analysis.

Quality of evidence: We assessed the quality of evidence across each outcome measure using the GRADE approach. We used a quality rating across studies that had four levels: high, moderate, low, or very low. We initially categorized RCTs as high quality but we could down- grade each trial after we assessed five criteria: risk of bias, consistency, directness, imprecision, and publication bias. Similarly, we initially categorized observational studies as low quality and we downgraded trials by these same criteria. However, in exceptional circumstances, we upgraded trials by three further criteria: large effect size, all plausible confounders would act to reduce the effect size, and evidence of a dose-response effect (Guyatt 2008).

RESULTS

Description of studies

Results of the search—We identified 2687 studies through the electronic search, and a further 195 from other sources (handsearching and contacting researchers in the field). We removed duplicates and screened all abstracts for possible inclusion. Of these, 520 unique studies were identified for full text screening (Figure 2).

Included studies—Thirteen studies met the inclusion criteria, and these are described in the Characteristics of included studies tables, and Table 2. Four studies were cluster-RCTs (Yapabandara 2001 LKA; Yapabandara 2004 LKA; Shililu 2007 ERI; Coulibaly 2011 MLI), eight studies were controlled before-and-after trials (Balfour 1936 GRC; Santiago 1960 PHL; Samnotra 1980 IND; Fillinger 2008 TZA; Sharma 2008 IND; Castro 2009 TZA; Fillinger 2009 KEN; Geissbühler 2009 TZA) and one study was a randomized crossover trial (Majambere 2010 GMB). None of the randomized studies made adjustments for clustering.

Seven studies were conducted in sub-Saharan Africa (urban Tanzania, rural Mali, rural Kenya, rural Gambia, and rural Eritrea), five studies in Asia (rural India, urban India, urban Philippines, and rural Sri Lanka), and one study in Europe (urban and rural Greece).

The studies targeted a variety of habitat types including both discrete habitats (such as drains, ditches, pits, ponds, and containers), and extensive habitats (such as rice paddies, swamps, and river flood plains).

The studies conducted in Africa targeted the major vectors *An. arabiensis* (the larval habitats of which were predominantly stream bed pools, canals, drainage channels, and wells in these studies), *An. gambiae* (drains and other man-made urban habitats, small streams and swamps, brick pits, ponds, tyre prints, flood plains, rice paddies, and other habitats associated with agriculture), and *An. funestus* (drains and other man-made urban habitats, small streams, and swamps). In Asia, the main vectors targeted were *An. fluviatilis* (streams), *An. culicifacies* (stagnant pools, ditches, irrigation channels, containers, wells, abandoned mine pits, and rice paddies), *An. stephensi* (containers, wells, rainwater pools, and canals), *An. minimus flavirostris* (streams), and *An. subpictus* (river bed pools, streams, irrigation ditches, and rice paddies). The study conducted in Europe targeted *An. elutus* and *An. superpictus* (manmade habitats).

One study conducted habitat modification alone (Sharma 2008 IND), two studies conducted habitat modification with larviciding (Balfour 1936 GRC; Shililu 2007 ERI), one study conducted habitat manipulation alone (Santiago 1960 PHL), two studies conducted habitat manipulation with larviciding (Samnotra 1980 IND; Castro 2009 TZA) and seven studies conducted larviciding alone (Yapabandara 2001 LKA; Yapabandara 2004 LKA; Fillinger 2008 TZA; Fillinger 2009 KEN; Geissbühler 2009 TZA; Majambere 2010 GMB; Coulibaly 2011 MLI).

LSM was not conducted by the community alone in any of the included studies. In seven studies, study staff conducted LSM in conjunction with specifically trained and employed members of the local community (Samnotra 1980 IND; Yapabandara 2001 LKA; Shililu 2007 ERI; Fillinger 2008 TZA; Geissbühler 2009 TZA; Majambere 2010 GMB; Coulibaly 2011 MLI). In one study, LSM was co-ordinated by study staff but actively conducted by specially trained and paid members of the local community, with local government support (Castro 2009 TZA). In one study, the government conducted LSM in conjunction with members of the local community (Sharma 2008 IND). In two studies, local (Balfour 1936 GRC) and foreign (Santiago 1960 PHL) government staff conducted LSM, and in two studies, study staff alone conducted LSM (Yapabandara 2004 LKA; Fillinger 2009 KEN).

Of the studies that recorded clinical outcomes, these were measured in children aged between six months to 10 years (Fillinger 2009 KEN; Majambere 2010 GMB), two years to 10 years (Santiago 1960 PHL), 0 years to five years (Geissbühler 2009 TZA) and of "school age" (Balfour 1936 GRC). Five studies recorded clinical outcomes in all age groups (Castro 2009 TZA; Samnotra 1980 IND; Sharma 2008 IND; Yapabandara 2001 LKA; Yapabandara 2004 LKA).

Excluded studies—We excluded 45 studies for the following reasons (see Characteristics of excluded studies table):

- Lack of control group (15 studies).
- Lack of one year of baseline data (two studies).
- Lack of baseline comparability between intervention and control areas (two studies).
- Uneven application of other malaria control interventions between intervention and control arms (for example, weekly active surveillance and treatment, chemoprophylaxis, indoor residual spraying) (six studies).
- Unable to locate full-text article (19 studies).
- Insufficient information reported to determine eligibility (one study)

We also excluded 481 studies for one or more of the following reasons (not included in the Characteristics of excluded studies):

- Did not study LSM as described in our methods.
- Did not report outcomes in either adult mosquitoes, human malaria or both.
- Did not have at least one year or one transmission season of data following the beginning of the intervention.
- Malaria control programme description in which LSM was one of many interventions.
- Review or opinion article.

Studies awaiting classification—We identified one potentially eligible study that did not report sufficient data to make a judgement about eligibility, and is therefore awaiting classification (Kinde-Gazard 2012).

Risk of bias in included studies—We have given a summary of our judgement of risks of bias in included studies in Figure 3. We listed individual risk of bias assessments in the Characteristics of included studies section.

Allocation—We judged all four cluster-RCTs at an unclear risk of selection bias due to an inadequate description of the method of randomization and allocation concealment (Coulibaly 2011 MLI; Shililu 2007 ERI; Yapabandara 2001 LKA; Yapabandara 2004 LKA). We judged the eight controlled before-and-after studies at high risk of selection bias due to the non-randomized design (Balfour 1936 GRC; Castro 2009 TZA; Fillinger 2008 TZA; Fillinger 2009 KEN; Geissbühler 2009 TZA; Samnotra 1980 IND; Santiago 1960 PHL; Sharma 2008 IND). We considered the cross-over trial to be at low risk of bias as each arm functioned as its own control (Majambere 2010 GMB).

Blinding—Due to the nature of the intervention, blinding of the implementers and the recipients was not possible, and we therefore classified all trials at high risk of performance bias.

Two cluster-RCTs only reported entomological data. As it would have been impossible to blind the data collectors, we classified these trials at high risk of bias (Coulibaly 2011 MLI; Shililu 2007 ERI). We judged two cluster-RCTs reporting clinical outcomes at unclear risk of detection bias (Yapabandara 2001 LKA; Yapabandara 2004 LKA). Two of the controlled before-and-after studies blinded the microscopists to allocation and we considered these trials at low risk of detection bias (Fillinger 2009 KEN; Geissbühler 2009 TZA). Three trials did not blind the microscopists to allocation and we considered these trials at high risk of detection bias (Balfour 1936 GRC; Fillinger 2008 TZA; Sharma 2008 IND). In three trials it was unclear if microscopists were blinded to allocation (Samnotra 1980 IND; Sharma 2008 IND; Castro 2009 TZA). The cross-over trial again blinded microscopists to allocation and we judged this trial at low risk of bias (Majambere 2010 GMB).

Incomplete outcome data—One cluster-RCT reported the loss of two clusters during the second year of the study (Coulibaly 2011 MLI). The remaining studies did not report losses to follow-up. We judged all trials to be at unclear risk of attrition bias.

Selective reporting—We judged two cluster-RCTs at high risk of reporting bias as they had evidence of selective reporting for entomological outcomes. The authors described several methods of data collection but they did not report all (Yapabandara 2001 LKA; Yapabandara 2004 LKA). We deemed two controlled before-and-after trials at high risk of selective reporting as they collected data on the whole population but only reported data on children (Castro 2009 TZA; Geissbühler 2009 TZA).

Baseline characteristics—We considered the cluster-RCTs at unclear risk of bias because they did not clearly report baseline characteristics. We considered four of the

controlled before-and-after studies at low risk of bias (Balfour 1936 GRC; Fillinger 2008 TZA; Sharma 2008 IND; Fillinger 2009 KEN) and four to be at unclear risk of bias (Santiago 1960 PHL; Samnotra 1980 IND; Castro 2009 TZA; Geissbühler 2009 TZA).

Contamination—We judged two cluster-RCTs at low risk of bias (Yapabandara 2001 LKA; Coulibaly 2011 MLI) and two trials at unclear risk of bias (Yapabandara 2004 LKA; Shililu 2007 ERI). We judged five controlled before-and-after trials at low risk of bias (Santiago 1960 PHL; Samnotra 1980 IND; Sharma 2008 IND; Fillinger 2009 KEN; Geissbühler 2009 TZA), two trials at high risk (Castro 2009 TZA; Fillinger 2008 TZA) and one trial at unclear risk of bias (Balfour 1936 GRC).

Incorrect analysis—We judged the four cluster-RCTs at high risk of bias because they did not adjust for clustering (Yapabandara 2001 LKA; Yapabandara 2004 LKA; Shililu 2007 ERI; Coulibaly 2011 MLI).

Other potential sources of bias—We considered the eight controlled before-and-after studies at high risk of confounding due to the study design (Balfour 1936 GRC; Santiago 1960 PHL; Samnotra 1980 IND; Fillinger 2008 TZA; Sharma 2008 IND; Castro 2009 TZA; Fillinger 2009 KEN; Geissbühler 2009 TZA).

Effects of interventions—See: **Summary of findings for the main comparison** LSM for controlling malaria

Comparison 1. Habitat modification alone versus control—One controlled before-and-after study, conducted in a rural, forested area of India, compared dam construction in one village with no intervention in two control villages (Sharma 2008 IND). The primary vector *An. culicifacies* was found breeding mainly in streams, stagnant pools, ditches, and irrigation channels. IRS was conducted annually in all villages.

Malaria incidence: At baseline, the incidence of malaria was twice as high in the treatment village than in the controls (Rate ratio 2.29, 95% CI 1.76 to 2.97, one study, 570 participants, Analysis 1.1). Following dam construction, the incidence of malaria in the treatment villages was reduced to similar levels as the control villages. In the treatment villages the incidence of malaria decreased from 638 to 262 cases per 1000 person years (one study, 570 participants, Analysis 1.1).

Parasite prevalence: At baseline, parasite prevalence did not significantly differ between treatment and control villages (one study, 570 participants, Analysis 1.2). Following dam construction, parasite prevalence significantly decreased in the treatment village compared to the controls (Risk ratio 0.23, 95% CI 0.12 to 0.43; one study, 570 participants, Analysis 1.2). Parasite prevalence in the treatment village decreased from 16% to 4%.

Comparison 2. Habitat modification with larviciding versus control—One cluster-RCT and one controlled before-and-after study conducted habitat modification with larviciding. The cluster-RCT, conducted in lowland and highland rural desert fringe areas of Eritrea, compared land filling and grading, drainage, and larviciding with *Bti* and temephos

with no intervention. The primary vector *An. arabiensis was* mainly found breeding in stream bed pools, canals, drainage channels, and wells (Shililu 2007 ERI).

The controlled before-and-after trial, conducted in urban and rural Greece, compared straightening, deepening and lining of streams, drainage and larviciding with Paris Green with no intervention. The main larval habitats of the major vectors *An. elutus* and *An. superpictus* were man-made habitats (Balfour 1936 GRC). Balfour 1936 GRC reported five years of post-intervention data (1931-1935) (Table 3) but only data for 1931 was included for the post- intervention period.

Parasite prevalence: In the controlled before-and-after study, parasite prevalence was lower at baseline in the treatment group (4%) than in the control group (9%) (Risk ratio 0.44, 95% CI 0.30 to 0.64; one study, 1737 participants, Analysis 2.1). Post-intervention, parasite prevalence remained low in the treatment group (6%) but increased substantially in the control group (24%) (Risk ratio 0.25, 95% CI 0.19 to 0.34; one study, 1538 participants, Analysis 2.1).

Splenomegaly prevalence: In the controlled before-and-after study, splenomegaly prevalence was again lower at baseline in the treatment group (27%) than in the control group (46%) (Risk ratio 0.58, 95% CI 0.51 to 0.66; one study, 1737 participants, Analysis 2.2). Post-intervention, splenomegaly prevalence decreased slightly in the treatment group (24%) and increased in the control group (57%) (Risk ratio 0.41, 95% CI 0.36 to 0.47; one study, 1538 participants, Analysis 2.2).

Adult mosquito density (measures other than human biting rate): The cluster-RCT only collected data on adult mosquito density (Shililu 2007 ERI) and did not report baseline data. Post- intervention the adult mosquito density decreased by 15.2% in the treatment group but the trial authors did not report if this reduction was statistically significant (Table 4).

Comparison 3. Habitat manipulation alone versus control—One controlled before-and-after study, conducted in an urban area of the Philippines, compared the construction of siphons for stream flushing in five areas of a town with no intervention in three areas (Santiago 1960 PHL). The main larval habitat of the primary vector *An. minimus flavirostris* was lake-fed streams. Two years of baseline data were reported (1952-1953), but we only included data from 1953 in the analysis. Data were presented for each of the five treatment and three control areas for total number of participants examined and total number of participants with parasitaemia or splenomegaly. We summed these data across areas and calculated a combined parasite and splenomegaly prevalence individually for treatment and control areas.

Parasite prevalence: In this study, parasite prevalence did not differ significantly at baseline between groups (one study, 847 participants, Analysis 3.1). Post-intervention, parasite prevalence was decreased significantly in the treatment village compared to the controls (Risk ratio 0.02, 95% CI 0.00 to 0.15; one study, 846 participants, Analysis 3.1), and decreased from 5.1% to 0.1% in the treatment village.

Splenomegaly prevalence: At baseline, splenomegaly prevalence was lower in the treatment group than the control group (Risk ratio 0.51, 95% CI 0.31 to 0.85; one study, 832 participants, Analysis 3.2). Post-intervention, there was a substantial reduction in splenomegaly prevalence in the treatment group compared to the control group (Risk ratio 0.02, 95% CI 0.00 to 0.17; one study, 846 participants, Analysis 3.2).

Adult mosquito density (measures other than human biting rate): Controlling for baseline differences, adult mosquito density decreased by 91% in the treatment group compared to the control group (Table 4). The trial authors did not report the statistical significance of this result.

Comparison 4. Habitat manipulation with larviciding versus control—Two controlled before-and-after trials conducted habitat manipulation with larviciding. One study, conducted in urban Tanzania (Dar es Salaam), compared clearance of vegetation and debris from drains in one site and larviciding with microbials in another site with a control site with no intervention. The primary vectors *An. gambiae* and *An. funestus* were mainly found breeding in man-made habitats, including drains (Castro 2009 TZA). The second study, conducted in an urban, desert fringe area of India, encouraged households to eliminate domestic larval habitats alongside larviciding with pirimiphos-methyl conducted by study staff. The main larval habitats of the primary vectors *An. culicifacies* and *An. stephensi* were containers, wells, and rainwater pools (Samnotra 1980 IND).

Malaria incidence: In one controlled before-and-after trial, baseline incidence did not significantly differ between treatment (64 cases per 1000 person years) and control groups (56 cases per 1000 person years) (97000 participants, one trial, Analysis 4.1). Post-intervention, the incidence was significantly lower in the treatment group (57 cases per 1000 person years) compared to controls (240 cases per 1000 person years at risk) (Rate ratio 0.24, 95% CI 0.22 to 0.25; one study, 97,000 participants, Analysis 4.1), due to a large increase in incidence in the control areas.

Parasite prevalence: While both studies collected data on parasite prevalence, only Samnotra 1980 IND reported the necessary data for inclusion in Analysis 4.2. Baseline parasite prevalence did not differ significantly between treatment and control groups (1887 participants, one study, Analysis 4.2). Post-intervention, parasite prevalence was significantly reduced in the treatment group compared to the control (Risk ratio 0.54, 95% CI 0.45 to 0.65; one study, 2713 participants, Analysis 4.2). Castro 2009 TZA did not report parasite prevalence in both treatment and control groups pre- and post-intervention, and therefore we could not include this trial in the analysis. The study reported a significant reduction in the odds of malaria infection in the post-intervention period compared to baseline in sites with habitat manipulation (drain clearance) (Odds ratio 0.23, 95% CI 0.14 to 0.38), with a greater effect observed when adjusted for age, rainfall, bed net use, and a short period of larviciding in addition to habitat manipulation (Odds ratio 0.12, 95% CI 0.05 to 0.3). The study also reported that post-intervention, the risk of infection was significantly higher in the habitat manipulation site compared to the control (Odds ratio 1.7, 95% CI 1.1 to 2.4) when adjusted for age, rainfall, bed net use, and a short period of larviciding in

addition to habitat manipulation. However, post-intervention, parasite prevalence did not differ significantly between larviciding and control sites (Castro 2009 TZA).

Adult mosquito density (measures other than human biting rate): Controlling for baseline differences, in one study adult mosquito density in the treatment group fell by 90% compared to the control group (Samnotra 1980 IND, Table 4). The trial authors did not report the statistical significance of this result.

Comparison 5. Larviciding alone versus control—Three cluster-RCTs, one randomized cross-over study, and three controlled before-and-after studies evaluated larviciding alone. Two cluster-RCTs were conducted in rural Sri Lanka, where larvicide (pyriproxyfen) was applied to larval habitats two to three times over a one year period. The main larval habitats of the primary vectors *An. culicifacies* and *An. subpictus* were abandoned gem mine pits (Yapabandara 2001 LKA) and river bed pools, streams, irrigation ditches, and rice paddies (Yapabandara 2004 LKA). The third RCT was conducted in Mali and reported entomological data only (Coulibaly 2011 MLI). Larvicide (*Bti* and *Bs*) was applied to larval habitats every one to two weeks for 18 months. The main larval habitats of the primary vector *An. gambiae* were brick pits, ponds, and tyre prints.

The controlled before-and-after studies were conducted in urban Tanzania (Fillinger 2008 TZA; Geissbühler 2009 TZA), and rural Kenya (Fillinger 2009 KEN). In Tanzania, *Bti* was applied weekly to open, sunlit habitats and *Bs* was applied every three months to closed habitats. The main larval habitats of the primary malaria vectors *An. gambiae* and *An. funestus* included man-made habitats associated with agriculture (rice paddies, sweet potato ridges, irrigation channels, and garden wells), construction and city drains, and natural pools and swamps associated with streams and high ground water level. In Kenya, a controlled before-and-after study compared weekly larviciding with *Bti* and *Bs* together with LLINs, with LLINs alone. The main larval habitats of the primary vectors *An. gambiae* and *An. funestus* were man-made drains, borrow pits, and swampy areas with low vegetation close to natural streams. A randomized cross-over study was conducted in The Gambia, where larviciding with *Bti* and *Bs* was carried out weekly. The main larval habitats of the primary vector *An. gambiae* were extensive, largely inaccessible flood plains and rice paddies (Majambere 2010 GMB).

Fillinger 2009 KEN reported baseline data for two long rainy seasons (April to June 2004; April to June 2005) and one short rainy season (November 2004 to January 2005). The trial authors reported post-intervention data for one long rainy season (April to June 2006) and two short rainy seasons (November 2005 to January 2006; November 2006 to January 2007). To allow comparability, we included data for one long and one short rainy season in the analysis for baseline and post-intervention periods. We included April to June 2005 and November 2004 to January 2005 in the baseline and April to June 2006 and November 2006 to January 2007 in the post-intervention data.

Malaria incidence: In the two cluster-RCTs from Sri Lanka, malaria incidence was comparable at baseline between the two groups (19981 participants, two studies, Analysis 5.1), and significantly reduced in the intervention group post-intervention (Rate ratio 0.26,

95% CI 0.22 to 0.31; 20124 participants, two studies, Analysis 5.1). The authors of these studies did not adjust the results for the effects of clustering, so we conducted a sensitivity analysis to assess the robustness of this result. The reduction in malaria incidence remained statistically significant even with a conservative ICC statistic of 0.1 (Rate ratio 0.25, 95% CI 0.06 to 0.98, Analysis 5.2).

In the before-and-after study from Kenya, the incidence of new parasitaemia was higher in the treatment group at baseline. However the difference was not significant (400 participants, one study, Analysis 5.1). Post-intervention, the incidence of new infections decreased in the treatment group compared to the control, but the difference was not statistically significant (Risk ratio 0.69, 95% CI 0.33 to 1.43, 663 participants, one study, Analysis 5.1).

Due to its cross-over design, we could not include the randomized cross-over study in the meta-analysis (Majambere 2010 GMB), and have presented the data separately (Table 5). Each of the four zones acted its own control. When we compared the intervention period with the non-intervention period for each zone, the effect of larviciding was inconsistent. Indeed, incidence appeared to decrease in all four zones between the first and second years of the study, regardless of the intervention. We found that this finding was consistent with the entomological data, which indicated that adult mosquito density and EIR decreased slightly across all zones between the two years (Table 6).

Parasite prevalence: In the cluster-RCT (Yapabandara 2001 LKA), baseline prevalence did not significantly differ between treatment and control groups (3351 participants, one study, Analysis 5.3), and prevalence decreased significantly in the treatment group post-intervention (Risk ratio 0.11, 95% CI 0.05 to 0.22, 2963 participants, one study, Analysis 5.3). In the sensitivity analysis, this reduction in parasite prevalence remained statistically significant with an ICC statistic of 0.01 (Rate ratio 0.13, 95% CI 0.03 to 0.56, Analysis 5.4), but became non-significant with the conservative ICC statistic of 0.1 (Analysis 5.4).

In the cross-over trial (which we excluded from the meta-analysis because of the cross-over design), we did not identify a consistent effect of larviciding on parasite prevalence across the four zones (Majambere 2010 GMB; Table 5). In the controlled before-andafter study, baseline prevalence was higher in the treatment group than the control group (Risk ratio 1.29, 95% CI 1.04 to 1.59, 2439 participants, one study, Analysis 5.3) and was significantly lower in the treatment group than the control group post-intervention (Risk ratio 0.60, 95% CI 0.42 to 0.87, 2374 participants, one study, Analysis 5.3).

Splenomegaly prevalence: In the cross-over trial, as with incidence and parasite prevalence, we did not identify a consistent effect of larviciding on splenomegaly prevalence across the four zones (Majambere 2010 GMB; Table 5).

EIR: In one cluster-RCT and three controlled before-and-after studies, the percent reduction in EIR ranged from 21% to 73% (Table 7). However, due to unreported data, we could neither calculate CIs nor take into account baseline density for all studies. We did not

identify any reduction in EIR in the randomized crossover study (Majambere 2010 GMB; Table 6).

Adult mosquito density (human biting rate): The percent reduction in density ranged from 31% and 73% in one cluster-RCT (Coulibaly 2011 MLI) and two controlled before-and-after studies (Fillinger 2008 TZA; Fillinger 2009 KEN; Table 8). However, we could not calculate CIs or take into account baseline density for all of these studies.

Adult mosquito density (density measures other than human biting rate): The percent reduction in density ranged from 34% to 91% in three cluster-RCTs (Yapabandara 2001 LKA; Yapabandara 2004 LKA; Coulibaly 2011 MLI) and one controlled before-and after trial (Fillinger 2009 KEN; Table 4). However, we could not calculate CIs for these studies and we could only account for differences at baseline in some studies. In one study there was no reduction in adult mosquito density in the treatment group compared to the control group (Majambere 2010 GMB; Table 6).

Comparison 6. Any LSM versus control

Malaria incidence: In two cluster-RCTs, LSM reduced malaria incidence by 74% in the treatment group compared to the control (Rate ratio 0.26, 95% CI 0.22 to 0.31; 20124 participants, two trials, Analysis 6.1, Figure 4). The interventions and settings of these two trials were similar therefore there was little heterogeneity between trials (I^2 = 12%).

In three controlled before-and-after trials, malaria incidence was not consistently reduced (98233 participants, three trials, Analysis 6.1), with variation in results (I^2 = 97%) possibly arising from significantly higher baseline incidence in the intervention areas compared to the controls in two trials. In both of these trials, LSM reduced malaria incidence in the intervention arm to levels similar to the control arm. As there were too few studies, we could not adequately investigate other potential causes of this heterogeneity. In one randomized cross-over trial, which we could not present in this analysis, incidence was not significantly reduced (Table 5). **Parasite prevalence:** In one cluster-RCT, LSM reduced parasite prevalence by 89% in the intervention group compared to the control (Risk ratio 0.11, 95% CI 0.05 to 0.22; 2963 participants, one trial, Analysis 6.2, Figure 5). In five controlled before-and-after trials, parasite prevalence was reduced by around two-thirds in the treatment groups compared to the controls (Risk ratio 0.32, 95% CI 0.19 to 0.55; 8041 participants, five trials, Analysis 6.2). In one randomized cross-over trial, parasite prevalence was not significantly reduced (Table 5). Statistical heterogeneity between these trials was high (I^2 = 89%), however this related to the magnitude rather than the direction of the effect. We could not investigate the potential causes of this heterogeneity as there were too few studies. In the single randomized cross-over trial, parasite prevalence was not significantly reduced (Table 5).

Splenomegaly prevalence: In two controlled before-and-after trials, cluster-RCTs, splenomegaly prevalence was 43% lower in the treatment group compared to the control (Risk ratio 0.57, 95% CI 0.50 to 0.65; 2569 participants, two trials, Analysis 6.3). In two controlled before-and-after trials, splenomegaly prevalence was not significantly reduced

(2384 participants, two trials, Analysis 6.3). In one randomized cross-over trial, splenomegaly prevalence was not significantly reduced (Table 5).

EIR: In four studies the percent reduction in EIR ranged from 21% to 84.6% (Table 7). However, we could not calculate CIs or take into account baseline density for one of these studies due to unreported data. In one study EIR increased in the control group from 0.00 to 2.92 in the second year of the intervention (Coulibaly 2011 MLI). In one study there was no reduction in EIR (Majambere 2010 GMB; Table 6).

Adult mosquito density (human biting rate): The percent reduction in density ranged from 31% and 73% in three studies (Table 8). We were not able to calculate CIs or take into account baseline density in two studies due to unreported data.

Adult mosquito density (measures other than human biting rate): The percent reduction in density ranged from 15% to 91% in seven studies (Table 4). However, we could not calculate CIs or take into account baseline density for all studies due to unreported data. In one study there was no reduction in adult mosquito density (Majambere 2010 GMB; Table 6).

We did not identify any trials that reported total under five year old mortality, time to infection, or prevalence of anaemia in children.

DISCUSSION

Summary of main results

We included four cluster-RCTs, eight controlled before-and-after trials, and one randomized cross-over trial in this review.

Malaria incidence

In two cluster-RCTs in Sri Lanka, larviciding of abandoned mines, streams, irrigation ditches, and rice paddies reduced malaria incidence by around three-quarters compared to controls (*moderate quality evidence*). In three controlled before-and-after trials in urban and rural India and rural Kenya, results were inconsistent (*very low quality evidence*). In one trial in urban India, the removal of domestic water containers together with weekly larviciding of canals and stagnant pools reduced malaria incidence by three quarters. In one trial in rural India and one trial in rural Kenya, malaria incidence was higher at baseline in intervention areas than in controls. However dam construction in India, and larviciding of streams and swamps in Kenya, reduced malaria incidence to levels similar to the control areas. In one additional randomized cross-over trial in the flood plains of the Gambia River, where larval habitats were extensive and ill-defined, larviciding by ground teams did not result in a statistically significant reduction in malaria incidence .

Parasite prevalence

In one cluster-RCT in Sri Lanka, larviciding reduced parasite prevalence by almost 90% (*moderate quality evidence*). In five controlled before-and-after trials in Greece, India, the

Philippines, and Tanzania, LSM resulted in an average reduction in parasite prevalence of around two-thirds (*moderate quality evidence*). The interventions in these five trials included dam construction to reduce larval habitats, flushing of streams, removal of domestic water containers, and larviciding. In the randomized cross-over trial in the flood plains of the Gambia River, larviciding by ground teams did not significantly reduce parasite prevalence.

Overall completeness and applicability of evidence

Effectiveness of LSM—Despite numerous historical reports on LSM programmes and examples of its effectiveness, such as the eradication of *An. gambiae* in Brazil and Wadi Haifa, Egypt (Soper 1943; Najera 2001), few trials have been conducted to rigorously evaluate the intervention and of these, very few are randomized studies. Our review therefore included non-randomized studies with adequate controls and baseline data. There is a lack of negative results among the nonrandomized trials and it is possible that we were unable to access studies with negative results due to publication bias. Trials were likely to have been conducted in environments in which experienced entomologists considered success likely. Thus the eligible studies may not reflect the likely impact of LSM in every habitat, but those in which it was deemed appropriate. Due to the small number of eligible studies, we were unable to construct funnel plots and assess the risk of publication bias or other sources of bias, such as poor study quality leading to artificially inflated effects in the smaller studies, selective outcome or analysis reporting, or chance. Also, we were unable to retrieve 19 full-text articles which may have introduced some bias.

However the included trials demonstrate that in carefully selected circumstances in various Asian and African settings, LSM can contribute to a reduction in incidence of clinical malaria, parasite prevalence, and splenomegaly prevalence. Our analysis was stratified by intervention type, and although each group contained only a small number of studies, the effect of LSM was relatively consistent suggesting that LSM can be effective when tailored appropriately to local ecology and infrastructure.

Feasibility of LSM—It is probable that LSM could be effective in most settings where adequate coverage of larval habitats can be achieved. What will change across settings therefore, is the feasibility and cost of achieving adequate coverage, which will depend on the number, type and ease of access of larval habitats, and the resources available. The included studies demonstrated large effects in Asia where larval habitats were relatively discrete and often man-made (for example, drainage ditches, pits, water storage containers, old mine pits, and irrigation channels), and also where larval habitats were more extensive, including rice paddies. All three included trials of LSM in urban Africa were conducted in Dar es Salaam, Tanzania, and demonstrated the protective effect of larviciding (and habitat manipulation) in this setting. In rural Africa, a significant reduction in clinical and entomological outcomes was observed in rural, highland Kenya, where larval habitats were confined to valley floors. In rural, lowland, savannah in Mali, a reduction in EIR, human biting rates, and other measures of adult mosquito density was observed. However, it is not known if the reductions were statistically significant or if human clinical outcomes were assessed. In rural, highland and lowland, desert fringe areas of rural Eritrea, a reduction in

adult mosquito density was observed. All of these studies demonstrate the potential impact of LSM in urban and rural Africa where habitats might be numerous but are relatively discrete and accessible.

In the flood plains of the Gambia River, where larval habitats were very numerous and ill-defined, hand and knapsack sprayer application of microbials by a ground team of 64 men was not associated with a reduction in malaria incidence, parasite prevalence, or splenomegaly. Clinical outcomes decreased in all zones over the two years of the study regardless of the intervention; an observation consistent with the entomological data. This study was conducted in an area where larval habitats in marshland stretched for several kilometres along the river, often two kilometres wide (Bogh 2003; Majambere 2008), making it difficult to cover the entire area with larvicides. Moreover, in this part of the country mosquitoes can fly long distances, often over two kilometres (Bogh 2007), making it likely that mosquitoes from non-intervention areas entered the study zones treated with larvicide. This area is not typical of rural sub-Saharan Africa where larval habitats are typically less extensive. We conclude that ground application of larvicide to areas of extensive flooding, such as the flood plains of major rivers or largescale rice irrigation projects, is not effective at reducing malaria transmission. Programmes including aerial spraying or large environmental management associated with the river and its flood plains may be able to address this limitation and could be evaluated.

The logistical feasibility of LSM is also affected by the type of intervention planned. In this review, we assessed larviciding, habitat manipulation, and habitat modification. While in practice these interventions may often be combined, each type of LSM is appropriate for different environmental conditions and has very different requirements. The majority of included trials carried out larviciding, which requires regular treatment of the majority of habitats within a target area. It is therefore labour intensive and needs a rigorous management system for application, surveillance, and evaluation. The type and quality of the larvicide product used is also an important consideration. Habitat manipulation may require regular maintenance but it would rarely require its own programme and management system. It may be integrated into ongoing activities, for example those of the ministries of public works or agriculture. Habitat modification is a more permanent approach and may be a one-time expense suited to specific settings, potentially those ill-suited to larviciding.

LSM should not be misconstrued as an intervention that can be set up and managed by the local community alone. Similar to IRS, it is an intervention that requires an intensive and carefully co-ordinated effort and the effort required to conduct LSM in the included studies was great. It is salient to note that LSM was not conducted by the local community alone in any of the included studies. Moreover, where members of the community were involved, they were actively trained, employed, and managed by study staff or the government. In general, the relative contributions of the community and ‘professionals’ were not well quantified. These measures of ‘coverage’ need to be taken into account and quantified in future studies.

Quality of the evidence—We appraised the quality of the evidence using the GRADE approach.

The two cluster-RCTs that reported clinical outcomes provide moderate quality evidence that larviciding, when applied appropriately, can have a large impact on the incidence and prevalence of malaria (Summary of findings for the main comparison). We downgraded this evidence from high because we had risk of bias concerns. Although they are described as randomized, neither study adequately described how intervention and control areas were selected. Since both studies were conducted in Sri Lanka, we considered downgrading the evidence further under 'directness' as the result could be considered poorly applicable to other settings. However, the evidence from the non-randomized trials from a wider variety of countries and eco-epidemiological settings indicates that where adult mosquito numbers are reduced, LSM will probably have important effects on malaria incidence and prevalence. The randomized trials did not adjust for the effects of clustering, therefore the 95% CIs presented are likely to be misleadingly narrow. However, our sensitivity analysis suggest that the results will probably remain statistically significant once clustering is taken into account and so we did not downgrade the evidence further. Moderate quality evidence implies that we can have reasonable confidence in these estimates of effect.

Potential biases in the review process

In most of the included trials, LSM demonstrated a major positive impact. LSM, chemoprophylaxis, and disease surveillance, were staples of many malaria control programmes between 1910 and 1940, prior to the DDT IRS era. LSM was reintroduced into some malaria control programmes with the advent of insecticide resistance. Many of the articles we reviewed were programme reports from the first half of the twentieth century when controlled trials were rare. Thus, we were not able to contact many of the authors. Our requests for unpublished studies were largely unfruitful, but it is possible that there exists a body of unpublished negative evidence with LSM. Some historical programme reports suggested that LSM was not particularly effective in some areas, especially in comparison to IRS with DDT (Mandekos 1948), but we did not include these trials as they did not meet the inclusion criteria. However, we were not able to locate many negative LSM studies and this is likely to be a significant source of bias in the review.

Agreements and disagreements with other studies or reviews

Peer-reviewed literature—This is the first Cochrane review of LSM. In general, our findings concur with the conclusions of other major LSM reviews. Takken 1990 described the notable success of LSM for malaria control in Indonesia before the advent of DDT and its relevance for malaria control today, especially in the light of insecticide and drugs resistance. Lindsay 2004 highlighted the potential role of LSM in integrated vector management in the East Asia and Pacific region. Both narrative reviews concur with the findings of our review because we found that LSM was effective at reducing malaria transmission in various Asian settings: urban India (Samnotra 1980 IND), urban Philippines (Santiago 1960 PHL), rural, forested and irrigated India (Sharma 2008 IND), and rural Sri Lanka (Yapabandara 2001 LKA; Yapabandara 2004 LKA).

Keiser 2005 conducted the first systematic review of the effect of environmental management on malaria and included studies where the intervention was predominantly or exclusively environmental management and the outcome was incidence of clinical malaria,

parasite prevalence, splenomegaly prevalence, or mortality rates. The authors excluded studies with entomological outcomes only or studies assessing the effect of LLINs. Overall, they included 40 studies, of which 85% (n = 34) were conducted before the era of the Global Malaria Eradication Campaign (1955 to 1969). They conducted a meta-analysis of sixteen trials of habitat manipulation and modification, with a reduction in risk of 88.0% (95% CI 81.7% to 92.1%) (of which the clinical malaria outcome being assessed was unclear). Our review was more systematic in its inclusion criteria and search strategy and we therefore included different studies.

Based on the premise that the environment mediates the effect of LSM, Keiser 2005 assigned studies to four eco-epidemiological settings: (1) malaria of deep forests, forest fringe, and hills; (2) rural malaria attributable to irrigation and large dams; (3) rural malaria attributable to wetlands, rivers, streams, coasts, and non-agricultural man-made water habitats; and (4) urban and periurban malaria. The review concluded that"malaria control programmes that emphasise environmental management are highly effective in reducing morbidity and mortality". The authors did not conduct any subgroup analyses to assess whether the effect differed across the four defined settings. We judge the quality of the data in the Keiser 2005 review to be poor, due in part to the inclusion of uncontrolled before-and-after studies. Our review concurs generally with the conclusions of Keiser 2005 but presents stronger evidence.

Walker 2007 highlighted that malaria control programmes in Africa have focused on targeting adult vectors and that renewed interest in LSM has been stimulated by concerns over insecticide resistance, rising costs of IRS, environmental impacts of interventions, and the move towards IVM. This review suggested that the use of LSM has been discouraged in sub-Saharan Africa due to the paucity of information on larval ecology and the ability of the major vector *An. gambiae* to breed in a variety of habitats. The authors reviewed large-scale field trials of LSM conducted in Africa between 1992 and 2007, which were described as limited in number. The review concluded that in particular settings where larval habitats are man-made or limited in number, such as in urban areas, LSM can be an effective intervention against malaria. In some rural settings, LSM might supplement LLINs or IRS, particularly during the dry season. LSM has minimal risk of environmental contamination or exposure of humans to pesticides. Our findings support the conclusions of Walker 2007. We similarly provide evidence that LSM is effective in select settings in sub-Saharan Africa, both rural and urban, where larval habitats are discrete and accessible.

Fillinger and Lindsay 2011 proposed that LSM will work best and be most cost-effective in areas where larval habitats are either seasonal, relatively few, where well-defined habitats are accessible by ground crews, or in cooler parts of the tropics where larval development is prolonged. The review authors suggest that these conditions occur frequently, and thus this method can be an effective tool for malaria control in selected eco-epidemiological conditions, such as areas of low to medium transmission intensity, areas of focal transmission, or epidemic prone areas. Such conditions are common in urban environments, desert fringe communities, highland settlements, and rural areas with high population densities. The review states that LSM is not a strategy for country wide application and should not be the primary tool selected in areas of intensive transmission. Nevertheless,

LSM has the potential to be integrated into control programmes after LLINs or IRS have reduced transmission to moderate or low levels of transmission. Therefore LSM should be considered in the consolidation phase of control and elimination programmes where it can be targeted in space and time. LSM may also be required for managing insecticide resistance and when outdoor transmission contributes substantially to overall transmission. Our review supports the finding that LSM can be effective in highland, urban, and desert fringe areas of Africa, and that ground application of larvicides may not be appropriate in areas with extensive flooding (such as the flood plains and paddy fields along the Gambia River).

Worrall and Fillinger 2011 recently concluded that the costs per person protected by LSM compares favourably with IRS and LLINs, especially in areas with moderate and focal malaria transmission where mosquito larval habitats are accessible and well defined. However, more data on the epidemiological impact of LSM is required to gauge the cost effectiveness of LSM. In such settings, it may be pragmatic to integrate LSM into existing control programmes. In our review we did not assess the cost-effectiveness or the overall cost of LSM.

WHO recommendations—In 2006, WHO made recommendations on the role of LSM based on its suitability in different eco-epidemiological settings (WHO 2006b). More recently, WHO recommendations specifically for larviciding state that “further evidence is needed of the value of larviciding as a routine and large-scale operation in both urban and rural areas” (WHO 2012). While this review concurs with aspects of the WHO position statement, in particular that more evidence is needed before definitive recommendations can be made regarding the appropriate use of LSM, there are several differences. The WHO position statement makes a comparison between the ratio of larval habitats to people in urban areas (low) and rural areas (high). We caution against such an urban-rural distinction since in some rural areas in Africa and elsewhere larval habitats may be equally limited in number, easily mapped, and accessed. While WHO does not generally recommend larviciding in rural sub-Saharan Africa unless particular circumstances limit larval habitats, this review provides evidence that larviciding in rural Africa may reduce malaria transmission, for example in rural Mali (Coulibaly 2011 MLI), rural Eritrea (Shililu 2007 ERI), and rural Kenya (Fillinger 2009 KEN). WHO recommends that “larviciding should be considered for malaria control (with or without other interventions) only in areas where the larval habitats are few, fixed and findable” (WHO 2012). While the extent to which larval habitats are ’findable’ may be important, this review found that larviciding may be effective where larval habitats are not necessarily few or fixed (Shililu 2007 ERI; Fillinger 2008 TZA; Castro 2009 TZA; Fillinger 2009 KEN; Geissbühler 2009 TZA; Coulibaly 2011 MLI).

AUTHORS’ CONCLUSIONS

Implications for practice

In Africa and Asia, LSM (when conducted in the manner and with the level of effort as in these trials) could be considered as another policy option alongside LLINs or IRS, or both, for reducing malaria morbidity in both urban and rural areas where a sufficient proportion of larval habitats can be targeted. Further large-scale studies are required to assess LSM effectiveness in rural areas of Africa where larval habitats are extensive. If applied in

appropriate locations with the required management and funding, LSM is likely to reduce malaria morbidity. Given the paucity of data regarding efficacy in many settings, LSM should be implemented with rigorous on-going surveillance of both entomological indicators and of human disease indicators to determine whether it is having the desired impact. This would also improve understanding of the potential benefit of LSM in addition to other vector control interventions, such as LLINs or IRS, or both.

Implications for research

Further cluster-RCTs of LSM in rural areas of Africa where larval habitats are extensive, although difficult and expensive to conduct, will improve the quality of the evidence. Research into the role of LSM (both larviciding and habitat modification and manipulation) in supplementing control measures that target adult vectors, in controlling malaria where insecticide resistance and outdoor vector biting are problematic, in targeting hotspots of transmission, and in malaria elimination programmes will be informative. Funding is needed to support this important research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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* Indicates the major publication for the study

PLAIN LANGUAGE SUMMARY

Mosquito larval source management for controlling malaria

What is larval source management and how might it work?

Malaria is an infectious disease transmitted from person to person by mosquitoes, and the main interventions insecticide treated bednets and indoor residual spraying reduce malaria infection by targeting adult mosquitoes. Larval source management (LSM) also aims to reduce malaria but instead targets immature mosquitoes, which are found in standing water, before they develop into flying adults. This is done by permanently removing standing water, for example by draining or filling land; making temporary changes to mosquito habitats to disrupt breeding, for example by clearing drains to make the water flow; or by adding chemicals, biological larvicides, or natural predators to standing water to kill larvae.

What does the research show?

We examined all the published and unpublished research up to 24 October 2012, and included 13 studies in this review.

Where larval habitats are not too extensive and a sufficient proportion of these habitats can be targeted, LSM probably reduces the number of people that will develop malaria (moderate quality evidence), and probably reduces the proportion of the population infected with the malaria parasite at any one time (moderate quality evidence).

LSM was shown to be effective in Sri Lanka, India, the Philippines, Greece, Kenya, and Tanzania, where interventions included adding larvicide to abandoned mine pits, streams, irrigation ditches and rice paddies where mosquitos breed, and building dams, flushing streams, and removing water containers from around people’s homes.

In one study from The Gambia where mosquitos were breeding in large swamps and rice paddies, spraying swamps with larvicide using ground teams did not show any benefit.

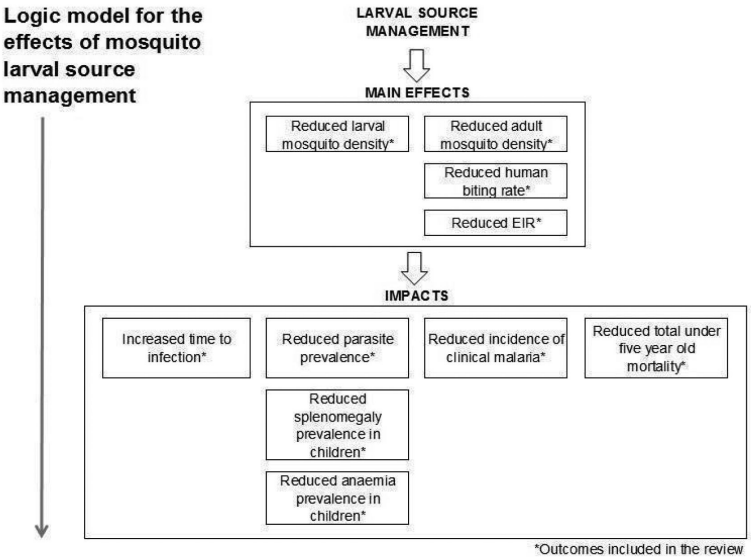

Figure 1.
Logic model for the effects of mosquito LSM on malaria

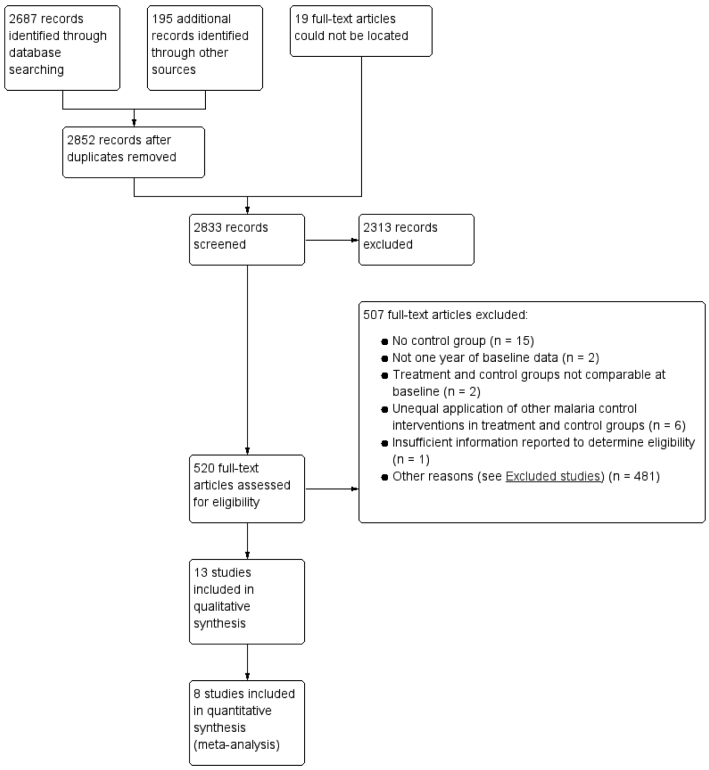

Figure 2.
Study flow diagram.

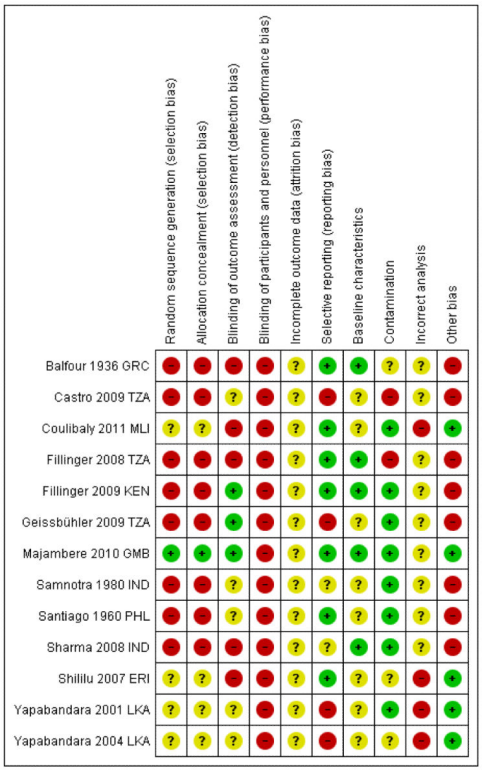

Figure 3.

Risk of bias summary: review authors' judgements about each risk of bias item for each included study.+ low risk of bias; - high risk of bias; ? unclear risk of bias.

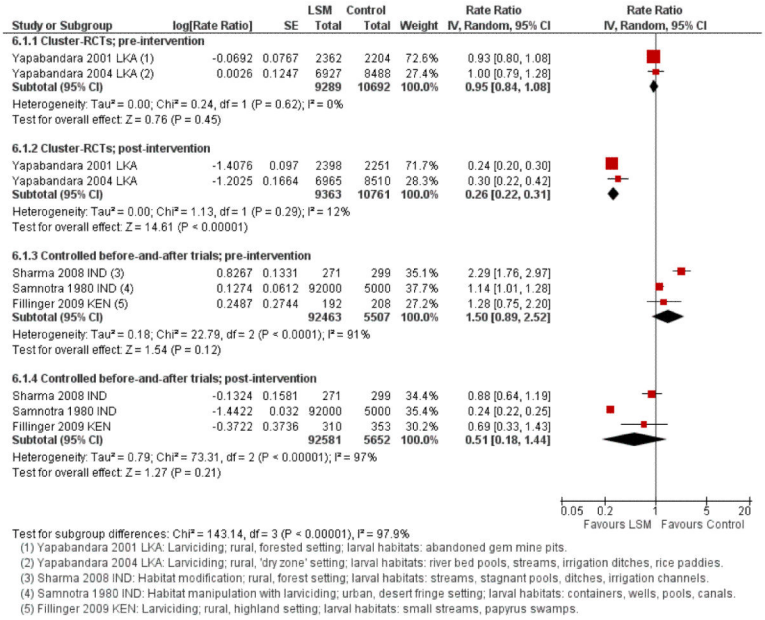

Figure 4.

Forest plot of comparison: 6 LSM versus control, outcome: 6.1 Malaria incidence.

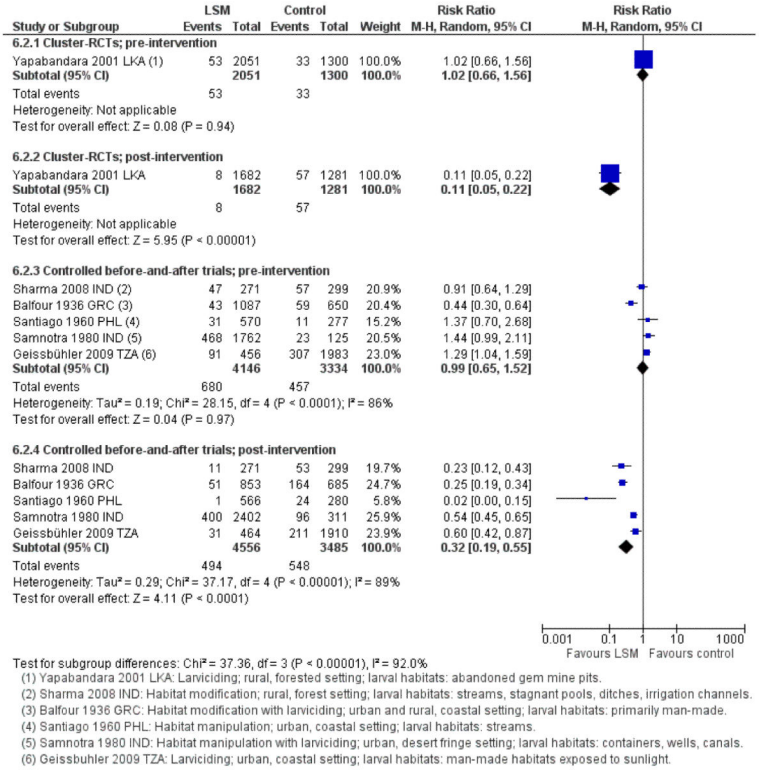

Figure 5.
Forest plot of comparison: 6. LSM versus control, outcome: 6.2 Parasite prevalence.

LSM for controlling malaria

Outcomes	Study Design	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evi-dence (GRADE)	Comments
		Assumed risk	Corresponding risk				
		Control	LSM				
Malaria incidence	**Cluster-RCT**	**65 per 1000**	**17 per 1000** (14 to 20)	**Rate Ratio 0.26** (0.22 to 0.31)	20124 (2 studies)	⊕⊕⊕O **moderate**[1,2,3,4]	The 95% CI may be falsely narrow as tri-als did not adjust for cluster design
	Controlled before-and-after	**232 per 1000**	**118 per 1000** (42 to 334)	**Rate Ratio 0.51** (0.18 to 1.44)	98233 (3 studies)	⊕OOO **very low**[5,6,7,8]	
Parasite prevalence	**Cluster-RCT**	**44 per 1000**	**5 per 1000** (2 to 10)	**Risk Ratio 0.11** (0.05 to 0.22)	2963 (1 study)	⊕⊕⊕O **moderate**[4,9,10]	The 95% CI may be falsely narrow as the trial did not adjust for cluster design
	Controlled before-and-after	**157 per 1000**	**50 per 1000** (30 to 86)	**Risk Ratio 0.32** (0.19 to 0.55)	8041 (5 studies)	⊕⊕⊕O **moderate** 11,12,13,14,15	

Patient or population: People living in malaria endemic areas

Settings: Urban or rural settings in Africa, Asia and Europe

Intervention: LSM

CI: Confidence interval; **RR:** Risk ratio.

* The basis for the **assumed risk** (for example, the median control group risk across studies) is provided in the footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).