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Title: EXPANDING THE VECTOR CONTROL TOOLBOX FOR MALARIA ELIMINATION: A SYSTEMATIC REVIEW OF THE EVIDENCE

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Abstract

Background

Additional vector control tools (VCTs) are needed to supplement insecticide-treated nets (ITNs) and indoor residual spraying (IRS) to achieve malaria elimination in many settings. To identify options for expanding the malaria vector control toolbox, we conducted a systematic review of the availability and quality of the evidence for 21 malaria VCTs, excluding ITNs and IRS.

Methods

Six electronic databases and grey literature sources were searched from January 1, 1980 to September 28, 2015 to identify systematic reviews, Phase I-IV studies, and observational studies that measured the effect of malaria VCTs on epidemiological or entomological outcomes across any age groups in all malaria-endemic settings. Eligible studies were summarized qualitatively, with quality and risk of bias assessments undertaken where possible. Of 17,912 studies screened, 155 were eligible for inclusion and were included in a qualitative synthesis.

Results

Across the 21 VCTs, we found considerable heterogeneity in the volume and quality of evidence, with seven VCTs currently supported by at least one Phase III community-level evaluation measuring parasitologically-confirmed malaria incidence or infection prevalence (insecticide-treated clothing and blankets, insecticide-treated hammocks, insecticide-treated livestock, larval source management (LSM), mosquito-proofed housing, spatial repellents, and topical repellents). The remaining VCTs were supported by one or more Phase II (n=13) or Phase I evaluation (n=1). Overall the quality of the evidence base remains greatest for LSM and topical repellents, relative to the other VCTs evaluated, although existing evidence indicates that topical repellents are unlikely to provide effective population-level protection against malaria.

Conclusions

Despite substantial gaps in the supporting evidence, several VCTs may be promising supplements to ITNs and IRS in appropriate settings. Strengthening operational capacity and research to implement underutilized VCTs, such as LSM and mosquito-proofed housing, using an adaptive, learning-by-doing approach, while expanding the evidence base for promising supplementary VCTs that are locally tailored, should be considered central to global malaria elimination efforts.

Introduction

Great advances have been made in malaria control and elimination, with a 37% global decline in malaria incidence during 2000-2015 (Global Malaria Programme, 2015). New targets include the elimination of malaria from at least 35 countries by 2030 (Global Malaria Programme, 2017), with renewed calls for eradication within a generation (Gates and Chambers, 2015). In sub-Saharan Africa (SSA), vector control with insecticide-treated nets (ITNs) and indoor residual spraying (IRS) has averted an estimated 524 million malaria cases since 2000 (Global Malaria Programme, 2015). However, after an extraordinary period of success in global malaria control, progress has stalled with 216 million malaria cases in 2016, up 5 million cases from 2015 (Global Malaria Programme, 2017). There remain important obstacles to achieving and sustaining progress towards elimination, including operational inefficiencies that lead to low effective coverage (Bhatt et al., 2015), insecticide resistance (Ranson and Lissenden, 2016), and residual transmission mediated by mosquito behaviours such as outdoor biting and resting, feeding upon animals, and early exit from houses immediately after entering, which are not effectively targeted by ITNs and IRS (Killeen; 2014, Govella and Ferguson, 2012).

To achieve malaria elimination goals in the face of such challenges, what evidence-based vector control tools (VCTs) can national malaria control and elimination programs access today or within the next decade to supplement ITNs and IRS? To date, ITNs and IRS are the only VCTs to have been recommended for wide-scale implementation by the World Health Organization (WHO), while larval source management (LSM) and personal protection measures against mosquitoes are recommended in some settings (World Health Organization, 2015). Recognising the need for additional VCTs, WHO recently established mechanisms for expedited vector control recommendations, including new technical expert panels (Malaria Policy Advisory Committee, 2015; WHO Vector Control Advisory Group, 2013) and the Innovation to Impact (I2I) initiative to support VCT development and access (Innovation to Impact (I2I), 2016). Recent calls for novel vector control interventions with proven effectiveness elevated the global demand for new VCTs (World Health Organization, 2017; malERA Refresh Consultative Panel

on Tools for Malaria Elimination, 2017). Here, to guide the identification of promising VCTs to expand the vector control toolbox for malaria elimination, we conducted a systematic review to collate published and unpublished evidence on the effect of selected VCTs on confirmed clinical malaria and malaria infection in people of any ages and on *Anopheles*-specific entomological outcomes in malaria-endemic regions. This is the first study to collate systematically the evidence across the spectrum of malaria vector control, excluding ITNs and IRS. Innovations in ITN and IRS technologies are also important contributions to the vector control toolbox (e.g. new active ingredients, insecticide combinations, and application technologies, among others) with significant product development and evaluation efforts underway but are outside the scope of this review (Innovative Vector Control Consortium, 2016; Wagman et al., 2018).

Methods

We conducted a systematic review of the literature to summarize the availability and quality of the evidence for 21 malaria VCTs, excluding ITNs and IRS (Table 1). We followed guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (Additional File 1) (Wilson et al., 2015). The candidate VCTs for evaluation were selected through consultation with experts (including a meeting held on June 1-3, 2015 in San Francisco, US) and the review of policy documents (WHO Vector Control Advisory Group, 2013; WHO Vector Control Advisory Group, 2014).

[Insert Table 1 here]

Eligibility criteria

Studies were included that evaluated any VCT targeting *Anopheles* mosquitoes in Table 1 and that met the eligibility criteria described in Table 2. Eligible study designs were categorized as observational, Phase I, Phase II, or Phase III studies. Observational studies included those with case-control, cohort or cross-sectional designs. Phase I studies were defined as laboratory assays to determine the mode of

action. Phase II were defined as semi-field, experimental hut, and small-scale field studies, generally with entomological outcomes. Finally, Phase III studies were defined as trials measuring the efficacy of the VCT against epidemiological outcomes under optimal conditions (Wilson et al., 2015). Categories based on level of evidence were used since level of evidence is the basis for WHO policy recommendation.

[Insert Table 2 here]

Search strategy and selection criteria

PubMed; EMBASE; LILACS; the Cochrane Infectious Diseases Group Specialized Register; Cochrane Central Register of Controlled Trials (CENTRAL), published in The Cochrane Library; and the Meta-Register of Controlled Trials (mRCT) were searched for studies published in English from January 1, 1980 to September 28, 2015 with the search terms described in Additional File 2. Search dates were restricted because systematic reviews included in this review captured the historical evidence on older VCTs, including LSM. Additionally, we searched reference lists of identified studies and contacted authors and field experts for unpublished data. To identify studies in progress, we searched the ClinicalTrials.gov registry. YAW and SH independently screened titles and abstracts, followed by full-text screening of relevant studies for eligibility using a standard form in Qualtrics (Qualtrics, Provo, UT). Disagreements were resolved by LST.

Data abstraction

Study characteristics (including participants, intervention, control group, outcomes, and sample size, as applicable) and findings were double-entered into a standard form in Microsoft Excel by YAW and verified by LST. Since we aimed to assess evidence availability, not VCT efficacy, we did not combine studies in a meta-analysis. Instead, for each VCT we summarized the current evidence by the number and type of completed studies and, where possible, stratified this information by outcome. We presented in tables all eligible studies for every VCT, except for VCTs with a recent (≤5 years old) high-quality

systematic review (Measurement Tool to Assess Systematic Reviews (AMSTAR) (Shea et al., 2007) score ≥50%; see below), for which we presented only the systematic review (Wilson et al., 2015).

Quality of systematic reviews and risk of bias in Phase III studies

The quality of systematic reviews was assessed using the AMSTAR tool (Shea et al., 2007). Risk of bias for randomized controlled trials (RCTs), controlled before-and-after studies (CBA), cross-over studies, and interrupted time-series studies was assessed using the Effective Practice and Organization of Care (EPOC) tool (Effective Practice and Organisation of Care (EPOC), 2015). Risk of bias was not assessed for Phase I, Phase II, or observational studies due to wide heterogeneity in study designs. We did not perform a statistical test for publication bias because we did not conduct any meta-analyses.

Results

The search results yielded 17,912 unique studies after removing duplicates (Figure 1). A total of 155 studies met the eligibility criteria and were included in the qualitative synthesis; these were of the following designs: systematic reviews (n=7); Phase III (n=7), Phase II (n=76), and Phase I (n=54) experimental studies; and cross-sectional (n=7), case-control (n=3), and cohort (n=1) observational studies (Figure 2, Additional File 3). Methodological quality was variable across the seven eligible systematic reviews, with AMSTAR scores ranging from 18% to 100% (Additional File 4A). The systematic reviews of LSM (n=2), mosquito-proofed housing (n=1), and topical repellents (n=1) were determined to be of the highest quality (AMSTAR scores ≥50%), while those of spatial repellents (n=2) and zooprophylaxis (n=1) were judged to be of lower quality. Of the 21 VCTs evaluated, we identified seven with one or more completed Phase III study, including some that were included in systematic reviews: LSM, insecticide-treated clothing and blankets, insecticide-treated hammocks, insecticide-treated livestock, mosquito-proofed housing, spatial repellents, and topical repellents; with recent, high-quality systematic reviews available for LSM, mosquito-proofed housing, and topical repellents (Table 3).

[Insert Figure 1 here]

[Insert Figure 2 here]

[Insert Table 3 here]

VCTs with a recent systematic review

Larval source management (LSM): A 2013 Cochrane review compared biological control with larvivorous fish to biological control without larvivorous fish (Walshe et al., 2013). No eligible studies included in this review measured malaria incidence, entomological inoculation rate (EIR), or adult vector density (Table 3). Nine quasi-experimental studies measured larval mosquito density, with variable effects. A second 2013 Cochrane review compared LSM (excluding biological control with larvivorous fish) with no LSM (Tusting et al., 2013). Compared to the control, LSM reduced malaria incidence by 74% in two cluster RCTs, but there was no consistent effect on malaria incidence in three CBA studies. GRADE quality (Atkins et al., 2004) of evidence ranged from very low to moderate. Parasite prevalence was reduced by 89% in another cluster-RCT and by an average of 68% in five CBA studies. GRADE quality of evidence was assessed to be moderate for both subgroups.

Mosquito-proofed housing: A 2015 systematic review included one Phase III RCT and four observational studies in a meta-analysis comparing screened with unscreened housing, in which findings on the effect on clinical malaria, malaria infection, and anaemia in children were inconsistent (Table 3) (Tusting et al., 2015). A further 15 observational studies were included in a meta-analysis comparing 'modern' housing (e.g. brick or cement walls and metal roofs) with 'traditional' housing (e.g. mud walls, thatched roofs, open eaves, and no screening) (Tusting et al., 2015). Modern housing was associated with a 45-65% lower odds of clinical malaria and 47% lower odds of malaria infection, compared to traditional housing, although the GRADE quality of evidence was assessed to be very low.

Topical repellents: In a systematic review of experimental studies comparing topical repellents with no repellent or placebo repellents (Wilson et al., 2014), the risk of *P. falciparum* malaria or infection was reduced by 18% in six RCTs and one CBA. *P. vivax* malaria or infection was reduced by 20% in five RCTs and one CBA, compared to the control, but neither reduction was statistically significant. EPOC risk of bias in the included studies ranged from low to unclear (Table 3).

Other VCTs with a Phase III evaluation

Insecticide-treated clothing and blankets: Malaria incidence was measured in two RCTs with low to moderate risk of bias, where the effect of insecticide-treated clothing and blankets ranged from an 81% decrease to no effect, compared to the control (Table 3) (Macintyre et al., 2003; Rowland et al., 1999). Outcomes assessed by the four Phase II studies included parasite prevalence (n=2) and adult mosquito mortality (n=2) (Additional File 3B).

Insecticide-treated hammocks: Malaria incidence and parasite prevalence were measured in two Phase III RCTs, with EPOC risk of bias for both studies assessed to be low (Table 3). In Venezuela, insecticide-treated hammocks reduced malaria incidence by 56% and parasite prevalence by 83%, compared to the control (Magris et al., 2007), and in Vietnam a greater reduction in malaria incidence and parasite prevalence was observed in the intervention arm than in the control (footnote to Table 3) (Thang et al., 2009). One Phase II study measured adult *An. gambiae* mortality, hut entry, and blood feeding inhibition (Additional File 3C).

Insecticide-treated livestock: Malaria incidence and parasite prevalence were measured in one Phase III cross-over study, with EPOC risk of bias assessed to be moderate, in which insecticide-treated livestock reduced malaria incidence by 31-56% and parasite prevalence by 40-54% compared to the control, though the effect was not consistently significant (Table 3) (Rowland et al., 2001). Entomological outcomes

186 measured in five Phase II studies included adult mosquito mortality and blood feeding preference
187 (Additional File 3C).
188
189 *Spatial repellents:* Two systematic reviews included laboratory and Phase II field studies only, with no
190 meta-analyses (Table 3) (Lawrence and Croft, 2004; Ogoma et al., 2012). No eligible studies measured
191 the effect of spatial repellents on malaria incidence. Parasite prevalence was measured in two RCTs, with
192 the EPOC risk of bias assessed to be low for both studies, and in one cross-sectional study. In the RCTs,
193 transfluthrin coils reduced parasite prevalence by 77% compared to long-lasting insecticide-treated nets
194 (LLINs) alone and by 94% when combined with LLINs, compared to no intervention in China (Hill et al.,
195 2014); metofluthrin mosquito coils reduced parasite prevalence by 52% compared to a placebo in
196 Indonesia (Syafruddin et al., 2014). Entomological outcomes measured in 23 Phase II studies and one
197 Phase I study included human biting rate (HBR), adult mosquito mortality, and repellency (Additional
198 File 3C).
199
200 ***VCTs with no Phase III evaluation***
201 Fourteen VCTs had Phase I, II, and/or observational evidence only: adult sterilization by contamination,
202 attractive toxic sugar baits (ASTBs), other attract-and-kill mechanisms, biological control of adult
203 vectors, eave tubes and eave baffles, endectocide administration in humans, endectocide administration in
204 livestock, genetic modification, insecticide-treated durable wall linings, insecticide-treated fencing,
205 larvicide application by autodissemination, push-pull systems, space spraying (ground application), and
206 zooprophylaxis (Figure 2, Additional File 3C, Additional File 3D). For these VCTs we included a total of
207 103 studies, comprising 42 Phase II, 51 Phase I, and 10 observational studies. All VCTs had at least one
208 eligible Phase II study, except endectocide administration in humans. Three VCTs had at least one
209 eligible observational study: endectocide administration in humans, spatial repellents, and
210 zooprophylaxis. For zooprophylaxis, we also identified one systematic review (AMSTAR score 18%),
211 which reported no meta-analysis (Donnelly et al., 2015). Entomological outcomes were measured for all

VCTs, while epidemiological outcomes were measured for two VCTs only (space spraying and zooprophylaxis).

Discussion

To address the challenges of insecticide resistance and residual transmission, strengthen malaria vector control, and maintain progress towards elimination, additional malaria vector control tools are needed. In this systematic review assessing the availability and quality of evidence for 21 supplementary VCTs, we included 155 studies dating from January 1, 1980 to September 28, 2015. This is the first study to collate evidence systematically across the malaria vector control toolbox beyond ITNs and IRS. Our study highlights the expanding pipeline of research into supplementary VCTs, while identifying substantial heterogeneity in the availability and quality of the evidence required by WHO to provide normative guidance on implementation (i.e. standardized epidemiological data from Phase III trials in multiple settings) (WHO Vector Control Advisory Group, 2013; Malaria Policy Advisory Committee, 2012).

For each VCT, we summarized the current evidence by the number and quality of studies and stratified this information by outcome where possible since this information forms the basis of WHO policy considerations. Within this framework, the evidence base was the most extensive for LSM and topical repellents, which both have multiple published Phase III evaluations and recent systematic reviews assessed to be of high methodological quality. While the evidence for LSM was assessed to be of very low to moderate quality (Tusting et al., 2013), combinations of larviciding and environmental management have been effective in reducing malaria transmission in certain eco-epidemiological settings in Africa and Asia and larviciding has been recommended by WHO as a supplementary intervention in SSA since 2013 (Global Malaria Programme, 2015). This recommendation is limited to discrete settings where habitats are relatively ‘few, fixed, and findable’; far narrower than settings in high-income countries where larviciding is used routinely and successfully for mosquito and disease control (Global Malaria Programme, 2015). In contrast, the evidence for topical repellents is of relatively high quality

(Wilson et al., 2014) but indicates that topical repellents are unsuitable as a large-scale public health intervention, although they can provide individual protection against mosquitoes (Wilson et al., 2014). We identified five further VCTs with at least one Phase III evaluation with epidemiological outcomes: insecticide-treated clothing and blankets, insecticide-treated hammocks, insecticide-treated livestock, mosquito-proofed housing, and spatial repellents. These VCTs offer additional options for supplementing ITNs and IRS, often with complementary modes of action. Further Phase III community level trials will help to clarify their roles in malaria vector control in different epidemiological settings (Killeen, 2014; Lobo NF et al. 2014; Pinder et al., 2016).

Our assessment of evidence was based on study design and outcomes, but in the future it may be necessary to consider evidence complementary to standard epidemiological assessments (Vontas et al., 2014). First, making recommendations across diverse transmission settings and local vector ecologies is difficult; what works in one or two settings may not work in all settings. Growing understanding of the genetic diversity among *Anopheles* further contributes to this complexity (The *Anopheles gambiae* 1000 Genomes Consortium, 2017). Trends in malaria transmission and performance of VCTs are also confounded by longer-term changes in environmental and infrastructural landscapes and climate (Snow et al., 2017). Although Cochrane reviews remain the gold standard in evidence-based policy, it is often inappropriate to combine findings from studies across different eco-epidemiological settings when VCT efficacy is tied to local transmission ecology (Walshe et al., 2013; Tusting et al., 2013). Second, some emerging VCTs remain years away from accumulating a full dossier of epidemiological evidence, and although further Phase III studies are planned (Thomas M et al., 2015), nearing completion (Mtove et al., 2016), or recently concluded (Homan et al., 2017), we identified fourteen VCTs for which no Phase III epidemiological data were available within the search dates. Demonstrating protection against disease and/or infection is critical before any VCTs can be recommended for large-scale deployment (Wilson et al., 2015). However, in some circumstances, evidence of effect might be built by adopting underutilised VCTs as supplementary interventions within a ‘learning-by-doing’ framework. This iterative, adaptive

approach involves the incorporation of rigorous monitoring and evaluation of epidemiological and entomological outcomes in control and intervention areas to support the gradual scale-up of additional VCTs within existing programme infrastructure, such as through adaptable Phase IV effectiveness studies (Killeen, 2014; Wilson et al., 2015; Global Malaria Programme, 2014). For example, while only one RCT of house screening for malaria control has been completed (Kirby et al., 2009), a large body of observational evidence suggests that screened housing is associated with reduced malaria risk and national malaria control programs are encouraged to explore opportunities to build 'healthier' housing (Roll Back Malaria, 2015). This approach would also allow for a more rapid expansion of the evidence base across a wider diversity of eco-epidemiological settings to inform locally-tailored solutions as well as iteration over time as the transmission landscape changes.

Direct transition to Phase IV 'learning-by-doing' approaches are controversial and inappropriate for VCTs with a poor or absent evidence base (Wilson et al., 2015). The history of ITNs and IRS demonstrates varying routes to establishing effectiveness against malaria disease or infection; ITNs underwent rigorous evaluation through Phase III RCTs (Darriet et al., 1984), while IRS effectiveness was established decades before evaluation in RCTs (Sadasivaia et al., 2007). Given adequate funding, promising new VCTs should reach approval far faster than ITNs, but depending on the entomological mode of action, efficacy of a VCT in one ecological setting is not always guaranteed elsewhere. Recent examples illustrate the importance of demonstrating efficacy against epidemiological as well entomological outcomes. Topical repellents reduce vector biting, but it took a cluster RCT with epidemiological outcomes to show their unsuitability as a generalizable public health intervention due to the high user compliance required (Messenger, 2012). Conversely, odour baited traps have recently been shown to reduce malaria infection prevalence in a rigorous RCT, but entomological data from that study suggest caution before deploying this VCT at scale in different settings since the traps were largely effective against *An. funestus* only (Homan et al., 2017).[36] Such information may be obtainable through 'learning-by-doing' evaluations, as long as evaluations of outcomes are of high quality. Research

institutions will need to support control programs in design, technical capacity, and analysis to ensure meaningful findings are obtained from Phase IV effectiveness evaluations. A recent call for more adaptive strategies responding to shifting transmission also highlights the need for optimizing combinations of interventions to maximize impact and mitigate the risk of insecticide resistance (malERA Refresh Consultative Panel on Tools for Malaria Elimination, 2017).

Despite limited evidence on their efficacy against malaria, the fourteen VCTs with no complete Phase III evaluation offer diverse modes of action to complement those of ITNs and IRS within a comprehensive intervention package. Some may only be suitable for niche application, for example, insecticide-treated clothing may be effective for individuals working outdoors at night, but not as a general public health intervention. Others such as insecticide-treated durable wall linings (which are impregnable with alternative insecticides to those used for IRS) might reduce reliance on the main classes of insecticides currently available for ITNs and IRS; a multi-country Phase III evaluation is currently underway (Messenger, 2012). Similarly, administration of endectocides such as ivermectin to people or livestock could circumvent insecticide resistance and target zoophagic behaviours in vectors, although epidemiological effect remains to be demonstrated (Chaccour et al., 2015; Foy et al., 2011). Some emerging VCTs might reduce transmission by vectors biting outdoors, including larvicide application by autodissemination using pyriproxyfen, which targets immature mosquitoes regardless of adult biting and resting behaviour (Mbare et al., 2014). Some emerging VCTs exploit vulnerability in alternative vector life stages to those targeted by ITNs and IRS. ATSBs, which target sugar feeding, consistently reduced adult mosquito density and HBR in Phase II studies in Israel, Mali, and the USA. However, Phase III trials of ATSBs with epidemiological outcomes are certainly needed. Genetic modification of mosquitoes aims to suppress populations thereby reducing vectorial competence (Alphey and Alphey, 2014), but our review highlights how such approaches have yet to progress fully beyond laboratory evaluations.

Overall the expansion of research on supplementary VCTs is encouraging, but arguably the first step to

316 strengthening vector control for malaria elimination is to improve operational capacity to deliver and
317 sustain existing interventions effectively (Brady et al., 2016). For example, major inefficiencies persist
318 within LLIN delivery systems across SSA, limiting population access (Bhatt and Gething, 2014). There
319 are also opportunities to explore new or improved delivery mechanisms for existing supplementary
320 interventions, such as aerial application of larvicides (Knapp et al., 2015). Some VCTs may not be highly
321 effective individually, but could potentially be highly effective when used in combinations. The malERA
322 updated research agenda highlights this need for optimizing combinations of interventions to maximize
323 impact and mitigate the risk of insecticide resistance (malERA Refresh Consultative Panel on Tools for
324 Malaria Elimination, 2017). Use of mathematical models could help to address such questions, where no
325 epidemiological evidence is available (Kiware et al., 2017). Critical to improving vector control is the
326 development of strong local entomological capacity (Mnzava et al., 2014), together with a much more
327 significant focus on community engagement and effective integration of control across vector-borne
328 diseases and government sectors (Brady et al., 2016; World Health Organization, 2009; World Health
329 Organization, 2017).
330
331 Our study has several limitations. First, our VCTs of interest were selected *a priori* through expert
332 consultation and are not an exhaustive list. Second, our search was restricted to English language papers
333 only, potentially excluding experiences from some regions. Third, we did not combine data across studies
334 in a meta-analysis, precluding evaluation of effect on entomological and epidemiological outcomes and
335 statistical tests for publication bias. Fourth, for studies with entomological outcomes there was no
336 mechanism to standardize outcomes and assess how heterogeneity in the choice of control affected study
337 findings. Fifth, this review focused on individual interventions and did not consider the potential benefits
338 of combining two or more of the new VCTs in communities already using ITNs and/or IRS. Finally, we
339 did not assess methodological quality and risk of bias in Phase I and II studies due to heterogeneity in
340 study design.
341

In conclusion, our review highlights the expanding pipeline of research into new and underutilized approaches to malaria vector control and the critical need to prioritize and fund robust evaluation of supplementary VCTs. Despite substantial gaps in the supporting evidence, several VCTs are promising supplements to ITNs and IRS. Strengthening operational capacity to implement and evaluate underutilized VCTs, such as LSM and mosquito-proofed housing, while expanding the evidence base for newer VCTs through strategic assessment of existing evidence and rigorous epidemiological evaluation, should be central to global malaria control and elimination efforts. A practical, program-oriented research agenda to evaluate where, when, and in what combination to use these supplemental VCTs should be developed and prioritized for funding and implementation in the near-term. Future research should also assess the cost, cost-effectiveness, scalability, and availability of supplemental VCTs to inform vector control strategies and intervention selection as countries and regions accelerate toward elimination.

Additional files

Additional file 1: PRISMA statement

Additional file 2: Search strategy

Additional file 3: Characteristics and summary of findings of systematic reviews, Phase I-III, and observational studies

Additional file 4: Quality assessment of systematic reviews and risk of bias in Phase III studies

Contributors

RDG, AT, and GFK conceived of the study. YAW, LST, RDG, GFK, and AT developed the study design. YAW, LST, and SH searched the literature. YAW and LST extracted the data and prepared the manuscript. PMG advised on the systematic review. All authors had access to study data and reviewed the final manuscript. All authors read and approved the final manuscript.

Author's information

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Conflict of interests

The authors declare that they have no conflict of interests. The study sponsors had no role in study design, in the collection, analysis and interpretation of data, in writing the report, and in the decision to submit for publication.

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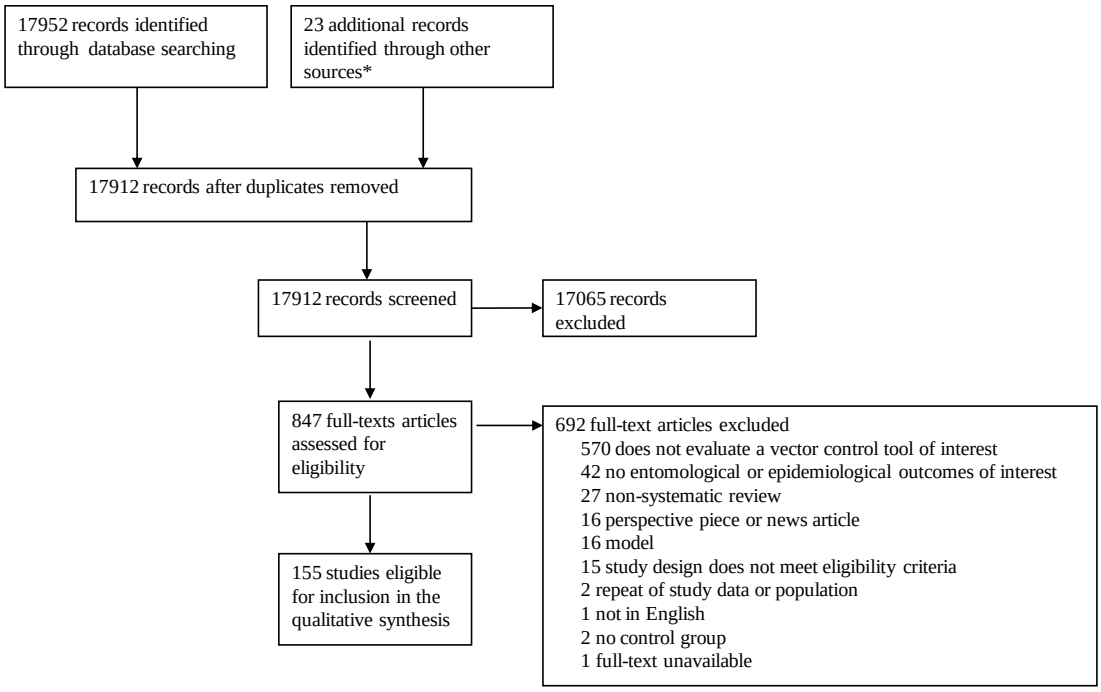

Figure 1. Study flow for a systematic review of the evidence for 21 malaria vector control tools
*Other sources: reference lists of included studies

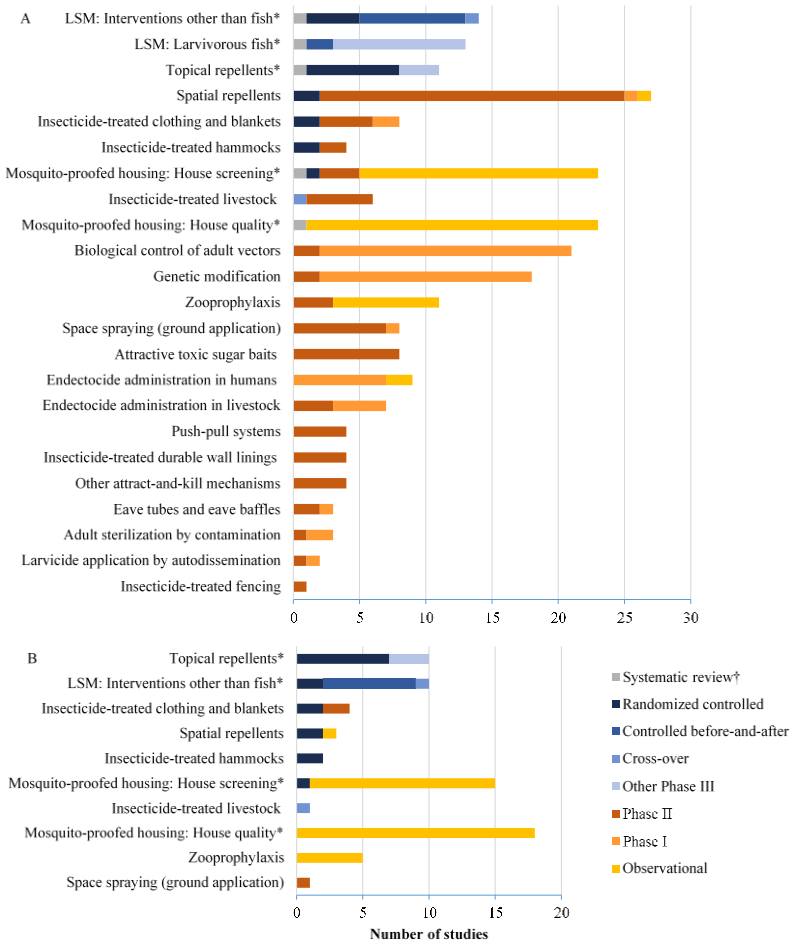

Figure 2. Frequency of eligible studies of 21 malaria vector control tools (VCTs), stratified by study design. A: studies with any outcome of interest; B: studies with diagnostically confirmed malaria incidence or prevalence. †Only systematic reviews with AMSTAR (A Measurement Tool to Assess Systematic Reviews14) scores of ≥50% are included. *For topical repellents, larval source management and mosquito-proofed housing, the frequency of studies represents all eligible studies within the referenced systematic review. For all other VCTs, the frequency of studies represents all eligible studies within the present review.

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Table 1. Description of malaria vector control tools (VCTs) included in the review

VCT*	Description	Primary mode(s) of action against malaria vectors
Interventions targeting immature mosquitoes		
Larval source management (LSM)	Management of potential larval habitats to prevent the development of immature mosquitoes into adults; includes habitat modification and manipulation; biological control with natural enemies of mosquitoes; aerial and ground-based larviciding.	Reduced adult emergence and density
Interventions targeting adult mosquitoes		
Adult sterilization by contamination	Sterilization of adult mosquitoes through contact with pyriproxyfen, using delivery mechanisms other than ITNs.	Reduced adult reproduction and density
Other attract-and-kill mechanisms	Traps and targets that attract blood-seeking mosquitoes using a combination of odours from humans and other mammals (e.g. carbon dioxide, L-lactic acid, ammonia and short-chain fatty acids), some of which are treated with chemical or biological insecticides (e.g. pyrethroids organophosphates, entomopathogenic fungi).	Increased adult mortality
Attractive toxic sugar baits (ATSB)	Lethal traps that exploit sugar-feeding behaviour to attract mosquitoes using sugar and that contain insecticides (e.g. boric acid).	Reduced adult survival and density
Biological control of adult vector capacity/longevity	Infection of adult mosquitoes with bacteria (e.g. Wolbachia spp) or entomopathogenic fungi to reduce longevity and/or up-regulate immune genes.	Reduced adult survival and infection rates
Eave tubes and eave baffles	A variety of different eave (space between the roof and walls of a house or structure) modifications that kill mosquitoes with traps or insecticides when they try to enter or exit from those houses.	Reduced adult survival and density
Endectocide administration in humans	Mass administration to humans of a systemic insecticide, sometimes described as an endectocide (e.g. ivermectin).	Reduced adult survival and density
Endectocide administration in livestock	Mass administration to livestock of an endectocide (e.g. ivermectin, fipronil, eprinomectin) to kill zoophagic *Anopheles*.	Reduced adult survival and density
Genetic modification	Mass release of mosquitoes, which are genetically modified (e.g. homing endonuclease genes (HEG) and RNA interference (RNAi); radiation-or chemo-sterilized males (sterile insect technique, SIT)).	Reduced adult reproduction and density and/or reduced competence as the primary host for malaria parasites
Insecticide-treated clothing and blankets	Clothing and/or blankets treated with an insecticide (e.g. permethrin)	Reduced adult survival and density, as well as human exposure to biting
Insecticide-treated durable wall linings	Thin, durable sheets of insecticide-treated cloths that cover interior wall surfaces; insecticides remain efficacious for a period of three to four years	Reduced adult survival and density
Insecticide-treated fencing	Insecticide-treated netting used as fencing around livestock enclosures	Reduced adult survival and density
Insecticide-treated hammocks	Hammocks treated with an insecticide (e.g. permethrin)	Reduced adult survival and density, as well as human exposure to biting
Insecticide-treated livestock	Application of topical insecticide (e.g. pyrethroids) or entomopathogenic fungus to livestock to kill zoophilic mosquitoes	Reduced adult survival and density
Mosquito-proofed housing	Houses with features that reduce mosquito house entry (e.g. use of modern wall, floor and roof materials, use of insecticide-treated or untreated door and window screens, presence of a ceiling).	Reduced human exposure to biting mosquitoes
Push-pull systems	The simultaneous use of attractive and repellent volatiles (e.g. baited trap near home with insecticide-treated fabric in eaves).	Reduced adult survival and density, as well as human exposure to biting
Space spraying (ground application)	Liquid insecticide (e.g. pyrethroids, malathion) dispersed as fine droplets in the air (either thermal or cold fog) using hand-held or vehicle-mounted devices; can be used indoors or outdoors. Includes targeted spraying of male mating swarms.	Reduced adult survival and density
Spatial repellents	Products that release chemical active ingredients into the air as vapours, which repel, incapacitate or kill adult mosquitoes (e.g. mosquito coils and emanators to release pyrethroids).	Reduced human biting, increased adult mortality
Topical repellents	Insect repellent (e.g. DEET, citronella, picaridin, lemon eucalyptus) applied to the skin to provide personal protection from biting.	Reduced human biting
Zooprophylaxis	Presence of animals/livestock to divert vector biting away from humans (which if applied at the individual level may also result in increased individual human risk, known as zoopotentiation).	Reduced exposure of humans to infectious adult mosquitoes and mosquitoes to infectious human beings
Interventions targeting immature mosquitoes via adults		
Larvicide application by autodissemination	Delivery of larvicide (e.g. pyriproxyfen) to larval habitats by adult female mosquitoes that are exposed to contaminated artificial resting sites	Reduced adult density

*VCTs excluded from the study: adult mosquito traps with no kill mechanism, aerial application of larvicide or adulticide, electronic mosquito repellents, indoor residual spraying, insecticide-treated curtains and nets, insecticide-treated paint, insecticide-treated plastic sheeting in tents or in temporary shelters, insecticide-treated tents, live plants as spatial repellents, nanoparticles for larviciding. Additionally, studies of the insecticidal properties of compounds and formulations were excluded.

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Table 2. Criteria for inclusion or exclusion of studies

	Inclusion Criteria	Exclusion Criteria
Study design	**Systematic reviews of experimental studies** **Phase III studies:** randomized controlled (RCT), controlled before-and-after (CBA)[*], cross-over[†], interrupted time-series[‡] **Phase II studies[§]:** small-scale, semi-field, experimental hut **Phase I studies:** laboratory **Observational studies:** case-control, cohort, cross-sectional	Review articles Opinion papers Modelling studies
Intervention	Any malaria vector control tool (VCT) targeting *Anopheles* mosquitoes described in Table 1	Adult mosquito traps with no kill mechanism, electronic mosquito repellents, indoor residual spraying (IRS), insecticide-treated curtains and nets, insecticide-treated paint, insecticide-treated plastic sheeting in tents or in temporary shelters, insecticide-treated nets (ITNs), insecticide-treated tents, live plants as spatial repellents, studies of the insecticidal properties of compounds and formulations
Primary epidemiological outcomes	Malaria incidence and infection prevalence in any age group, diagnostically confirmed by microscopy or rapid diagnostic test	Malaria incidence and infection prevalence not diagnostically confirmed by rapid diagnostic test or microscopy
Primary entomological outcomes	Entomological inoculation rate (EIR)[¶] Human biting rate (HBR)[‖] Adult mosquito density metrics other than HBR**	
Secondary entomological outcomes[††]	Additional entomological outcomes appropriate to the intervention including adult mosquito fecundity, adult mosquito fitness, adult emergence rates, knockdown post-exposure, blood-feeding inhibition	
Dates	Studies published from January 1, 1980 to September 28, 2015	Studies published before January 1, 1980 and after September 28, 2015

[*]Controlled before-and-after studies: if arms were comparable at baseline, there were at least two units per arm, follow-up periods were the same for the intervention and control arms, and baseline characteristics were comparable between arms.

[†]Cross-over studies: if there was adequate allowance for washout (time between two intervention periods to allow the effect of the first intervention to be washed out).

[‡]Interrupted time-series studies: if data were collected during at least three time points pre- and post- follow-up, if no co-interventions were introduced after baseline data collection and if the intervention was implemented for a clearly defined period.

[§]Phase III studies were differentiated from Phase II studies in being conducted in real-life settings (not semi-field or experimental hut systems) and having a minimum intervention period of one transmission season or year.

[¶]Entomological inoculation rate (EIR): the number of bites by sporozoite-infected mosquitoes per person per unit time.

[‖]Human biting rate (HBR): the number of host-seeking mosquitoes attempting to attack humans per person or house per time period.

[**]Density measures other than HBR (e.g. number of mosquitoes per person, house or catch), measured directly using human landing catches or indirectly using light traps, knock-down catches or other methods of biting rate determination.

[††]Secondary entomological outcomes, such as adult mosquito fecundity, adult mosquito fitness, adult emergence rates, knockdown post-exposure, blood-feeding inhibition, were included where reported in Phase I and II studies.

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