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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, 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.[1,2] New targets include the elimination of malaria from at least 35 countries between 2015 and 2030,[1] with renewed calls for eradication within a generation.[3] 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.[2] However, there remain important obstacles to achieving and sustaining elimination, including operational inefficiencies that lead to low effective coverage,[4] insecticide resistance,[5] 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.[6,7]

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.[1] Recognising the need for additional VCTs, WHO recently established mechanisms for expedited vector control recommendations, including new technical expert panels,[8] and the recently-formed Innovation to Impact (I2I) initiative also aims to support VCT development and implementation.[9,10] 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.

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).[11] 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.[9,12]

[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.[13]

[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)[14] score ≥50%; see below), for which we presented only the systematic review.[13]

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

The quality of systematic reviews was assessed using the AMSTAR tool.[14] 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.[15] 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.[16] 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.[17] 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 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).[18] 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).[18] 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,[19] 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).[20,21] 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,[22] 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).[23] 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).[24] Entomological outcomes measured in five Phase II studies included adult mosquito mortality and blood feeding preference (Additional File 3C).

Spatial repellents: Two systematic reviews included laboratory and Phase II field studies only, with no meta-analyses (Table 3).[25,26] No eligible studies measured the effect of spatial repellents on malaria incidence. Parasite prevalence was measured in two RCTs, with the EPOC risk of bias assessed to be low for both studies, and in one cross-sectional study. In the RCTs, transfluthrin coils reduced parasite prevalence by 77% compared to long-lasting insecticide-treated nets (LLINs) alone and by 94% when combined with LLINs, compared to no intervention in China;[27] metofluthrin mosquito coils reduced parasite prevalence by 52% compared to a placebo in Indonesia.[28] Entomological outcomes measured in 23 Phase II studies and one Phase I study included human biting rate (HBR), adult mosquito mortality, and repellency (Additional File 3C).

VCTs with no Phase III evaluation

Fourteen VCTs had Phase I, II, and/or observational evidence only: adult sterilization by contamination, attractive toxic sugar baits (ASTB), other attract-and-kill mechanisms, biological control of adult vectors, eave tubes and eave baffles, endectocide administration in humans, endectocide administration in livestock, genetic modification, insecticide-treated durable wall linings, insecticide-treated fencing, larvicide application by autodissemination, push-pull systems, space spraying (ground application), and zooprophylaxis (Figure 2, Additional File 3C, Additional File 3D). For these VCTs we included a total of 103 studies, comprising 42 Phase II, 51 Phase I, and 10 observational studies. All VCTs had at least one eligible Phase II study, except endectocide administration in humans. Three VCTs had at least one eligible observational study: endectocide administration in humans, spatial repellents, and zooprophylaxis. For zooprophylaxis, we also identified one systematic review (AMSTAR score 18%), which reported no meta-analysis.[29] Entomological outcomes were measured for all VCTs, while epidemiological outcomes were measured for two VCTs only (space spraying and zooprophylaxis).

Discussion

To strengthen malaria vector control and maintain progress towards elimination, additional malaria vector control tools are needed to supplement ITNs and IRS. 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).[9,30]

For each VCT, we summarized the current evidence by the number and quality of studies and stratified this information by outcome where possible. 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,[17] 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.[2] 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.[2] In contrast, the evidence for topical repellents is of relatively high quality[19] but indicates that they are unsuitable as a large-scale public health intervention, although they can provide individual protection against mosquitoes.[19] 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.[6,31,32]

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.[33] First, making recommendations across diverse transmission settings and local vector ecologies is difficult. 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.[16,17] Second, some emerging VCTs remain years away from accumulating a full dossier of epidemiological evidence, and although further Phase III studies are planned,[34] nearing completion,[35] or recently concluded,[36] 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.[13] However, in some circumstances evidence of effect might be built by adopting underutilized VCTs as

supplementary interventions within a 'learning-by-doing' framework. This iterative 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.[6,13,37] For example, while only one RCT of house screening for malaria control has been completed,[38] 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.[39]

Direct transition to Phase IV 'learning-by-doing' approaches are controversial and inappropriate for new VCTs or VCTs with a poor evidence base.[13] 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,[40] while IRS effectiveness was established decades before evaluation in RCTs.[41] 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.[42] 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.[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.

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.[43] 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.[44,45] 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.[46] 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,[47] 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 strengthening vector control for malaria elimination is to improve operational capacity to deliver and sustain existing interventions effectively.[48] For example, major inefficiencies persist within LLIN delivery systems across SSA, limiting population access.[49] There are also opportunities to explore new or improved delivery mechanisms for existing supplementary interventions, such as larviciding.[50] Some VCTs may not be highly effective individually, but could potentially be highly effective when used in combinations. Use of mathematical models could help to address such questions, where no epidemiological evidence is available. Critical to improving vector control is the development of strong local entomological capacity,[51] together with better integration of control across vector-borne diseases and

288 government sectors.[48,52]

289

290 Our study has several limitations. First, our VCTs of interest were selected *a priori* through expert
291 consultation and are not an exhaustive list. Second, our search was restricted to English language papers
292 only, potentially excluding experiences from some regions. Third, we did not combine data across studies
293 in a meta-analysis, precluding evaluation of effect on entomological and epidemiological outcomes and
294 statistical tests for publication bias. Fourth, for studies with entomological outcomes there was no
295 mechanism to standardize outcomes and assess how heterogeneity in the choice of control affected study
296 findings. Fifth, this review focused on individual interventions, and did not consider the potential benefits
297 of combining two or more of the new VCTs in communities already using ITNs and IRS. Finally, we did
298 not assess methodological quality and risk of bias in Phase I and II studies due to heterogeneity in study
299 design.

300

301 In conclusion, our review highlights the expanding pipeline of research into new and underutilized
302 approaches to malaria vector control and the critical need to fund robust evaluation of supplementary
303 VCTs. Despite substantial gaps in the supporting evidence, several VCTs are promising supplements to
304 ITNs and IRS. Strengthening operational capacity to implement and evaluate underutilized VCTs, such as
305 LSM and mosquito-proofed housing, while expanding the evidence base for newer VCTs through
306 strategic assessment of existing evidence and rigorous epidemiological evaluation, should be central to
307 global malaria elimination efforts.

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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