Revolutionizing Vector Control for Malaria Elimination

A systematic review of vector control tools

Key Messages

- A systematic review of the availability and quality of evidence for 21 malaria vector control tools (VCTs), excluding insecticide-treated nets (ITNs) and indoor residual spraying (IRS), found an expanding pipeline of research into supplementary VCTs, while identifying important gaps in the evidence base for many promising VCTs
- Among the 21 VCTs evaluated, the quality and size of the evidence base remains relatively highest for larval source management (LSM) and topical repellents, although existing evidence indicates that topical repellents are unlikely to provide effective protection against malaria
- Supplementary VCTs are needed immediately to accelerate global malaria elimination efforts, but most VCTs remain years away from accruing the epidemiological evidence traditionally required by the World Health Organization for policy recommendations
- Research to narrow important evidence gaps is critical, but malaria elimination programs could also consider the adoption of carefully selected VCTs within a learning-by-doing framework that retains rigorous evaluation with epidemiological outcomes

Additional Vector Control Tools Are Needed to Accelerate Progress to Malaria Elimination

The scale-up of insecticide-treated nets (ITNs) and indoor residual spraying (IRS) as the primary vector control tools contributed to an estimated 524 million averted malaria cases in sub-Saharan Africa (SSA) and the 37% global decline in malaria incidence during 2000–2015.[1,2] Vector control using ITNs and IRS is integral to achieving global malaria targets, yet the future impact and sustainability of these tools are threatened by operational inefficiencies and low effective coverage.[3] Where optimal ITNs or IRS coverage has been achieved, persisting transmission linked to insecticide resistance[4] or residual transmission stand in the way of countries reaching their malaria elimination goals.[5,6]

To achieve malaria elimination in the face of such challenges, what evidence-based vector control tools (VCTs) can national malaria control and elimination programs access today or soon, to supplement ITNs and IRS? To date, ITNs, IRS, and larval source management (LSM) are the only VCTs to undergo rigorous evaluation against malaria resulting in a policy recommendation by the World Health Organization (WHO).[7] Despite extensive field testing (Phase III randomized controlled trials with epidemiological outcomes), it took 25 years to achieve the large-scale roll out of ITNs that we see today.[8]

To guide the identification of promising, supplementary VCTs to support malaria elimination, the UCSF Global Health Group's Malaria Elimination Initiative (MEI) led a systematic review to evaluate 21 existing and emerging malaria VCTs, excluding ITNs and IRS.[9] It is the first systematic review of its kind.

Systematic Review of Supplementary Vector Control Tools

The MEI conducted a systematic review of the availability and quality in the evidence base for 21 supplementary VCTs selected by experts in the field, excluding ITNs and IRS (Appendix 1). The review also highlights priority research areas in vector control for malaria elimination.

The systematic review includes studies that evaluated any of the 21 VCTs, that were of any study design, listed in Appendix 2, and that evaluated any outcome of interest, including malaria incidence and infection prevalence in any age group (diagnostically confirmed by microscopy or rapid diagnostic test) and levels of mosquito transmission using entomological metrics. Studies that were published from January 1, 1980 to September 28, 2015 were included. Evidence for each VCT was summarized by the number and type of studies and, where possible, stratified by outcome.

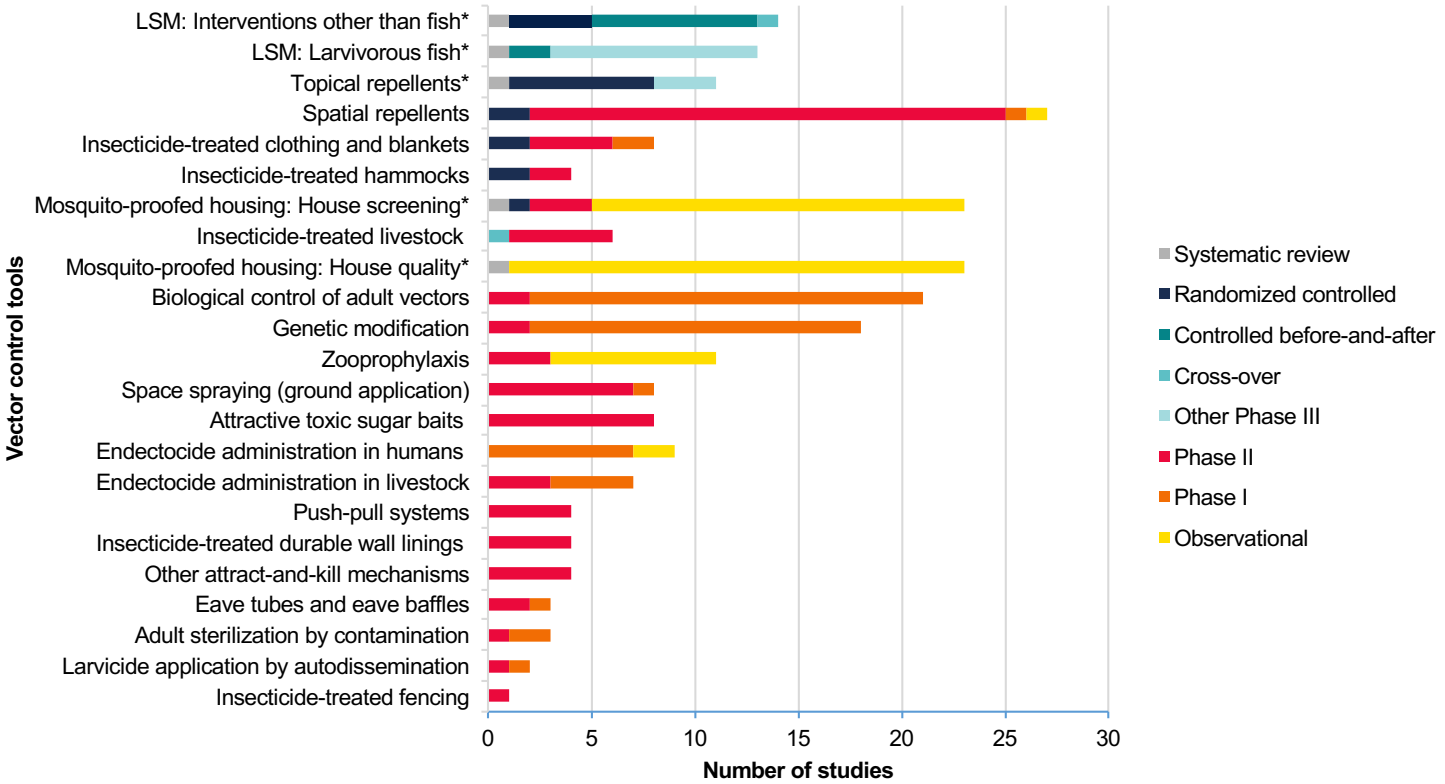
Few Tools Have Advanced to Phase III Trials and Policy Recommendations

Of 17,912 studies screened, 155 were eligible for inclusion.

- The volume and quality of evidence across VCTs was variable. Seven VCTs were supported by at least one Phase III community-level evaluation, considered the strongest level of experimental evidence (see Appendix 2), with epidemiological outcomes and varying levels of impact on malaria (Figure 1).
- Of the seven VCTs with at least one Phase III community-level evaluation, the quality and size of the evidence base remains relatively highest for LSM and topical repellents, although existing evidence indicates that topical repellents are unlikely to provide effective population-level protection against malaria.
- The remaining VCTs were supported by at least one Phase II or Phase I evaluation (n=14) (Figure 1), showcasing the rich pipeline of research into further VCTs that remain at earlier stages of evaluation.

Figure 1. Frequency of eligible studies for 21 vector control tools (VCTs), stratified by study design

The quality of existing evidence in support of each VCT is illustrated by the number of eligible studies of different designs. We considered the strength of evidence to be highest in systematic reviews of intervention studies (grey) and Phase III community-scale studies (blue shades) and less strong for small-scale field, laboratory, and observational studies (red and yellow shades) (Appendix 2). *Only systematic reviews assessed to be of high methodological quality are shown.



Tools with a Strong Evidence Base are Ready for Implementation, Others Continue to Build Evidence

- Some VCTs with a strong evidence base, such as LSM, are ready for implementation as appropriate based on local conditions. Further VCTs may be ready for implementation in the near-term, while other VCTs remain years away from accumulating the epidemiological evidence traditionally required for a policy recommendation by the WHO.
- However, it is important to note that quality of the evidence does not equate to efficacy against malaria, and, while larviciding has been recommended as a supplementary malaria intervention in certain settings by the WHO since 2013,[10] existing evidence indicates that topical repellents are unlikely to provide effective protection against malaria.[11]
- Existing Phase II and Phase I evidence can guide malaria control programs in exploring innovative vector control approaches appropriate to local vector ecology, and catalyze operational research in 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 program infrastructure.

Expand the Epidemiological Evidence Base while Accelerating Introduction through a "Learning-by-Doing" Approach

- Strengthen capacity and financing to implement operationally ready yet underutilized VCTs, such as LSM, that have a strong evidence base.
- Expand the epidemiological evidence base for emerging VCTs through Phase III evaluations with epidemiological outcomes.
- Recognizing that countries need access to supplementary, evidence-based VCTs to move towards ambitious elimination goals, support malaria control programs in exploring the adoption of carefully-selected VCTs within a learning-by-doing framework.

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The **Malaria Elimination Initiative (MEI)** at the University of California San Francisco (UCSF) Global Health Group believes a malaria-free world is possible within a generation. As a forward-thinking partner to malaria-eliminating countries and regions, the MEI generates evidence, develops new tools and approaches, disseminates experiences, and builds consensus to shrink the malaria map. With support from the MEI's highly-skilled team, countries around the world are actively working to eliminate malaria—a goal that nearly 30 countries will achieve by 2020.

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Appendix 1. Guide to Malaria Vector Control Tools Included in the Review

VCT*	Description
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 larviciding.
Interventions targeting adult mosquitoes	
Adult sterilization by contamination	Sterilization of adult mosquitoes through contact with pyriproxifen, using delivery mechanisms other than ITNs
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)
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)
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
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
Endectocide administration in humans	Mass administration to humans of a systemic insecticide, sometimes described as an endectocide (e.g. ivermectin)
Endectocide administration in livestock	Mass administration to livestock of an endectocide (e.g. ivermectin, fipronil, eprinomectin) to kill zoophilic *Anopheles*
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))
Insecticide-treated clothing and blankets	Clothing and/or blankets treated with an insecticide (e.g. permethrin)
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
Insecticide-treated fencing	Insecticide-treated netting used as fencing around livestock enclosures
Insecticide-treated hammocks	Hammocks treated with an insecticide (e.g. permethrin)
Insecticide-treated livestock	Application of topical insecticide (e.g. pyrethroids) or entomopathogenic fungus to livestock to kill zoophilic mosquitoes
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)
Push-pull systems	The simultaneous use of attractive and repellent volatiles (e.g. baited trap near home with insecticide-treated fabric in eaves)
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 and includes targeted spraying of male mating swarms
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)
Topical repellents	Insect repellent (e.g. DEET, citronella, picaridin, lemon eucalyptus) applied to the skin to provide personal protection from 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)
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

*VCTs excluded from the study: adult mosquito traps with no kill mechanism, 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. Additionally, studies of the insecticidal properties of compounds and formulations were excluded.

Appendix 2. Guide to Study Designs Included in the Review

Systematic reviews of experimental studies provide the strongest evidence. Categories of experimental study are ranked from 'A' (strongest evidence) to 'C' (least strong evidence). Adapted from Wilson[12] and GRADE.[13]

Systematic review	Review of all scientific evidence for a specific intervention that applies strategies to limit bias in the assembly, appraisal and synthesis of relevant studies, including pre-defined eligibility criteria, an explicit search strategy and a meta-analysis where possible. 'Gold-standard' reviews are produced by the Cochrane Collaboration.
Experimental studies	**A. Phase III**: Randomized controlled trials, controlled before-and-after studies, cross-over studies, interrupted time-series studies. Conducted in real (not semi-field or experimental hut) settings; intervention period is at least as long as one year or one transmission season. **B. Phase II**: Small-scale field, semi-field and experimental hut studies; intervention period is less than one year or one transmission season. **C. Phase I**: Laboratory assays to determine the mode of action.
Observational studies	Case-control, cohort and cross-sectional studies