Priorities for Broadening the Malaria Vector Control Tool Kit

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Long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS) have contributed substantially to reductions in the burden of malaria in the past 15 years. Building on this foundation, the goal is now to drive malaria towards elimination. Vector control remains central to this goal, but there are limitations to what is achievable with the current tools. Here we highlight how a broader appreciation of adult mosquito behavior is yielding a number of supplementary approaches to bolster the vector-control tool kit. We emphasize tools that offer new modes of control and could realistically contribute to operational control in the next 5 years. Promoting complementary tools that are close to field-ready is a priority for achieving the global malaria-control targets.

Vector Control and Malaria
The World Health Organization (WHO) recently published its Global Technical Strategy for Malaria 2016–2030, which sets out a vision and strategic framework for reducing malaria transmission by at least 90% over the next 15 years, and preventing its re-establishment in countries that are currently free of malaria [1]. Vector control is a central pillar within this Global Technical Strategy, reflecting the fact that wide-scale deployment of long-lasting insecticide-treated bed nets (LLINs, see Glossary) and indoor residual spraying (IRS) with insecticides have contributed to substantial declines in the burden of malaria in the past 15 years [1,2]. However, the robustness and utility of current vector control faces two key biological challenges. First, the negative impacts of insecticide exposure on survival and reproduction impose strong selection for resistance [3]. This problem is exacerbated by the fact that there is a very limited selection of chemical insecticides approved for public health use; at present, pyrethroids are the only class of insecticides used on a wide scale on bed nets, and they account for two-thirds of the total product (by area) used in IRS for malaria control [4]. Accordingly, physiological (and, to a lesser extent, behavioral) resistance is now widespread across mosquito species and populations, threatening the effectiveness of the frontline insecticide-based interventions [1,5]. Second, the current core tools are most effective against Anopheles vectors that feed and rest indoors and exhibit a preference for feeding on human hosts during night-time [2]. Yet, in many locations, vectors exhibit more diverse behaviors, feeding on other hosts, feeding and resting outdoors, and/or feeding in the early evening [6–8]. A consequence of both of these challenges is that there are limits to how much LLINs and IRS alone can reduce transmission, even with further intensification and optimization [9]. This problem creates a pressing need for supplementary vector-control tools.

Exploration of vector-control tools is a rich area of research. A recent review commissioned by the United States President’s Malaria Initiative highlighted examples of 12 broad technologies/approaches for new interventions, including new types of LLIN with resistance-breaking properties. Another recent analysis evaluated the evidence for 21 existing and emerging
vector-control tools excluding LLINs and IRSii. Other reviews have focused on more specific strategies, such as biologically based or transgenic approaches [10,11]. Given these recent articles, our aim here is not to conduct an exhaustive review of prospective control tools. Rather, we outline two key criteria that we consider important in prioritizing the development of supplementary vector-control tools: a mode of action that is complementary to current tools, and a short timeline for implementation. Based on these criteria, we highlight a handful of tools/approaches that we feel have greatest immediate potential to add to the malaria vector-control tool kit.

Timeline to Impact
As described above, the WHO Global Technical Strategy for Malaria 2016–2030 aims to reduce malaria transmission by at least 90% over the next 15 years. Similar ambitious targets are set out in the Aspiration to Action document prepared by the Bill and Melinda Gates Foundationi, which calls for a halving in transmission every 10 years, leading to ultimate eradication by 2040. Intercountry alliances, such as the Asia Pacific Malaria Elimination Network, aim for regional elimination by 2030iv.

The Global Technical Strategy is informed by a modeling analysis which explores a range of future intervention scenarios that vary in terms of access to vector control (LLINs and IRS) and drug treatments (both seasonal malaria chemoprevention and first-line treatments with artemisinin combination therapy) [9]. The modeling analysis reveals a number of key insights (Figure 1). First, if vector control and drug use remain at current levels, malaria mortality is expected to increase in the next 10–15 years due to a changing immunity profile in the population, wherein people born after the current interventions were scaled up are exposed more slowly and acquire their first and subsequent cases at an older age. Second, if the effectiveness of existing tools falls (e.g., through evolution of resistance) the rebound in malaria burden will likely be more pronounced. Third, further intensification of existing core tools to 80 or 90% coverage can lead to reductions in malaria burden, and even elimination in some settings, but would fail to reach the anticipated targets in areas of intense transmission. Finally, only if supplementary tools are forthcoming within the near future is it predicted that the WHO targets can be achieved.

The requirement for supplementary tools to be implemented at scale within the next 5 or so years puts an emphasis on approaches that are close to field-ready, and limits the immediate utility of prospective tools that are still far from operational (Figure 1). For example, there is considerable interest in the potential of new gene-editing technologies for developing transgenic mosquitoes for use in population-replacement or population-suppression strategies [12–15]. Approaches to reduce vector competence by manipulating elements of the mosquito microbiome [16–18], or via transfection with endosymbionts such as Wolbachia [19,20], are also being examined. However, given the current exploratory nature of this research (in most cases the research has yet to progress beyond laboratory-based proof-of-principle studies), together with the challenges and timelines of regulatory approval, it is questionable whether such technologies will achieve wide-scale operational use for malaria control within the next 8–10 years. This argument does not mean that these technologies cannot make valuable contributions somewhere down the line. Nonetheless, it is very difficult to see how they can play a substantial role in averting the present-day insecticide-resistance crisis, or in driving down malaria transmission in the next decade (Figure 1).

Complementing Existing Vector Control
Because transmission of malaria is so directly linked to the bite of the mosquito, a lot of research focuses on blood feeding behavior and factors affecting vector competence. Yet the life cycle of the adult mosquito involves much more than taking and digesting a blood meal.

Glossary

Anthropophilic: a preference for feeding on humans and resting in and around domestic dwellings.

Behavioral resistance: changes in vector feeding or resting behavior that reduce insecticide exposure.

Community-wide effect: a reduction in transmission risk at community level even though only a certain proportion of the community is protected directly by an intervention. It occurs, for example, when an intervention kills mosquitoes and so reduces the vector–human contact for the whole community.

Entomological inoculation rate (EIR): a measure of human exposure to infectious mosquitoes defined as the number of infectious bites received by a person over a given time period (usually a year).

Gonotrophic cycle: describes a life cycle of alternate feeding and laying eggs. The duration of the gonotrophic cycle is defined as the number of days that gravid mosquitoes take to lay their eggs after taking a blood meal.

Indoor residual sprays (IRS): spraying the walls and other surfaces of a house with a residual insecticide that is designed to kill mosquitoes as they rest after blood feeding.

Integrated vector management (IVM): the optimal use of diverse tools, tactics, and resources to reduce transmission of disease by vectors.

Long-lasting insecticide-treated net (LLIN): a bed net coated or impregnated with insecticide that is designed to remain effective for 3–5 years and 20 washes.

Physiological insecticide resistance: reduced susceptibility to an insecticide by changes in basic physiology, including target-site mutations that reduce neuronal sensitivity, and metabolic mechanisms that enhance detoxification.

Residual transmission: malaria transmission that persists after full operational coverage with effective LLIN and/or IRS interventions has been achieved.

Vector competence: physiological and behavioral characteristics that shape a vector’s capability to transmit a pathogen (i.e., become infected following an infectious blood meal, successfully harbor the...
A young adult mosquito emerges from the aquatic larval habitat with a small reserve of energy [21]. Both male and female mosquitoes then consume sugars, mainly obtained from floral and extrafloral nectar, and honeydew [22]. Mating does not occur for a couple of days after the adults emerge. Males form mating swarms and virgin females enter these swarms, locate a male, and then exit as a couple to mate [23]. To complete the first gonotrophic cycle, most female mosquitoes must next take a blood meal. The host could be a human or, depending on the feeding behavior, an alternative vertebrate such as a cow [24]. Feeding can take place indoors or outdoors depending on the species and their populations [6]. To digest a blood meal safely, and before the onset of searching for an oviposition site, a female will rest for 2–4 days. Resting can take place indoors or outdoors, again depending on the species [25]. After blood digestion, a female has to find a suitable oviposition site, which, in some cases, can be distant and take several days to locate, during which time there is likely more demand for sugars [26]. Because human malaria parasites take around 8–12 days to complete the sporozoite cycle within the mosquito under optimum temperatures (and this can be considerably longer under
suboptimal conditions) [27,28], female mosquitoes must survive at least three such gonotrophic cycles before being able to transmit malaria [29] (Figure 2).

All of these mosquito activities, and the locations in which they take place, provide opportunities for disrupting the adult mosquito’s life cycle, and hence, reducing transmission. LLINs and IRS work by lowering the contact rate between humans and vectors, either because the insecticide changes the normal feeding or host-searching behavior (repellency or deterrence) [30], and/or the insecticide causes mosquito death, affecting the age structure of the mosquito population and potentially the adult mosquito density [31]. Because of the importance of these core tools, and the potential for insecticide resistance to render them less effective, development of next-

Figure 2. Diverse Behaviors and Activities of Adult Malaria Mosquitoes as They Progress From Emergence Through to Egg Laying Over One or More Gonotrophic Cycles. Adult mosquitoes emerge from aquatic habitats (1) and mate within a few days (2), potentially taking a sugar meal for energy (*). Male mosquitoes then tend to die quite quickly, while females go in search of a blood meal (3). Blood feeding could be on a diversity of hosts, either indoors or outdoors. After blood feeding, the mosquitoes will tend to rest for 2–4 days while they digest the blood to produce eggs (4). Resting can occur in a range of indoor or outdoor environments. Once the eggs are fully developed the mosquitoes then search for a suitable oviposition site (5), potentially taking another sugar meal (*) to boost energy reserves for flight. Once a suitable aquatic habitat is located and the eggs are laid, female mosquitoes can repeat the blood feeding and egg production process over subsequent days to complete multiple gonotrophic cycles.

Current core vector-control tools (long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS)) target female mosquitoes at just two points in the adult life cycle within domestic dwellings only.
generation LLIN and IRS products comprising novel active ingredients, that overcome resistance, is an important ongoing activity [32]. Nevertheless, LLINs and IRS target only mosquitoes inside the domestic dwelling, leaving activities such as sugar feeding, mating, outdoor biting, host searching and house entry, alternate host feeding, outdoor resting, etc. untouched (Figure 2). Also, LLINs and IRS generally impact only females. Supplementary tools that target adult mosquitoes more broadly, at multiple points across their life cycle, are needed to complement these established tools and, in so doing, address the challenge of residual transmission and create new opportunities for insecticide-resistance management.

**Candidate Tools**

In Table 1 we provide an illustrative (not exhaustive) list of adult vector-control tools that are currently being researched (i.e., have been published on in recent years) and assess them according to our criteria of ‘field-ready’ and ‘complementary’. We also outline briefly some of the challenges we face in order to move forward to operational use. This assessment is somewhat subjective, but our aim is to highlight technologies that bring something new to the table (Figure 2) and identify a feasible timeline for implementation (Figure 1). Below, we discuss in more detail a number of tools/approaches that we feel have greatest immediate utility.

**Sugar Feeding**

Attractive toxic sugar baits (ATSBs), which utilize a mixture of an oral toxin, natural sugars, and floral attractants to lure mosquitoes [33,34], take advantage of the natural propensity of both male and female mosquitoes to sugar feed. ATSBs can be used in outdoor bait stations or indoor bait stations, or they can be sprayed directly onto nonflowering vegetation [35–37]. The products appear inexpensive and require minimal change in user behavior [38]. Moreover, the wide choice of candidate stomach toxins creates options for control of mosquitoes resistant to the currently used contact insecticides [39].

A small-scale field trial in Mali showed that ATSBs sprayed onto vegetation reduced the population of *Anopheles gambiae* s.l. by 90% [40]. A similar study in the Rift Valley showed a 95% reduction in female *Anopheles sergentii* populations, while completely eradicating males [41]. Even with indoor bait stations, both male and female mosquitoes were attracted to, and fed from, this source, with more than 90% reduction in populations [38]. Moreover, these studies report changes in population age structure towards younger mosquitoes; this is an important result as it is the old mosquitoes that are responsible for transmission. A recent modeling study showed that ATSBs could substantially reduce *An. gambiae* populations and associated entomological inoculation rates (EIRs) to near zero, in both sugar-resource-rich and sugar-resource-poor environments [42]. Evaluating this prediction empirically, and exploring the full range and potential usage of ATSBs in future integrated vector-control strategies more generally, are key next steps.

**Swarm Sprays**

Another underexploited target for vector control is swarming behavior [43]. The locations of mating swarms are stable over the seasons [44] and appear linked to swarm markers on the ground, such as wells, wood piles, or the limits between footpaths and grass [45,46]. These markers seem to provide visual cues for the males [43]. The proposed strategy for targeting these swarms is to use field observations and Geographic Information Systems (GIS) [43,47] to map swarm locations and then spray swarms with insecticide when they start forming, just after sunset. The swarms are generally accessible, as they are only 1–3 m above the ground, depending on the swarm markers [45,46].

A recent field trial conducted in Burkina Faso recruited a team of 20 volunteers from a village and targeted 300 swarm locations, spraying swarms with aerosols as they appeared over a
<table>
<thead>
<tr>
<th>Control tool</th>
<th>Complementary mode of action</th>
<th>Field-ready technology</th>
<th>Estimated time to use</th>
<th>Challenges</th>
<th>Refs</th>
</tr>
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<tbody>
<tr>
<td>Attractive toxic sugar bait</td>
<td>YES: Targets both sexes of diverse mosquito species; repeated exposure across life time; independent of blood feeding or resting behavior; resistance-breaking actives.</td>
<td>YES: Ongoing small-scale field trials; simple technology with available products.</td>
<td>0–5 years</td>
<td>Short lifespan when used as sprays on vegetation; further work needed to evaluate in different ecological contexts and to optimize within integrated vector management (IVM) strategies; nontarget evaluation.</td>
<td>[33–42]</td>
</tr>
<tr>
<td>Swarm sprays</td>
<td>YES: Targets males and also pregravid females; independent of blood feeding or resting behavior; resistance-breaking actives.</td>
<td>YES: Ongoing small-scale field trials; simple technology with available products.</td>
<td>0–5 years</td>
<td>Large number of swarm targets; demonstrate impact across diverse species and ecosystems; needs optimization within IVM; cost evaluations and implementation strategies required (who sprays and who pays?).</td>
<td>[43–49]</td>
</tr>
<tr>
<td>Housing improvement</td>
<td>YES: Prevents house entry and protects users without LLINs; independent of insecticide resistance; potential for resistance-breaking actives in Eave Tubes.</td>
<td>YES: Numerous available approaches and new technologies (like Eave Tubes) under large-scale field evaluation; existing field trials and meta-analyses support impact; housing improvement is already happening across many disease-affected countries.</td>
<td>0–5 years</td>
<td>Further research required on appropriateness in different socioeconomic settings; need for cost-effectiveness evaluations and exploration of different implementation strategies.</td>
<td>[50–67]</td>
</tr>
<tr>
<td>Livestock targets</td>
<td>YES: Addresses problem of zoophilic vectors.</td>
<td>YES: IRS of livestock structures can use existing technology; numerous topical insecticides and endectocides on the market.</td>
<td>0–5 years</td>
<td>Need for longer lasting endectocides to reduce treatment frequency; not all livestock are treatable or have defined housing structures; cost and effectiveness across different systems and socioeconomic contexts.</td>
<td>[68–82]</td>
</tr>
<tr>
<td>Spatial repellents</td>
<td>YES: Potentially protects users before they go indoors, and users without LLINs.</td>
<td>YES: Certain products already commercially available and used.</td>
<td>0–5 years</td>
<td>Need for improved long-lasting products; costs likely prohibitive in certain settings and require financial contribution from end-user (consumer products not covered by normal public health budgets); appropriate targeting and optimizing within IVM.</td>
<td>[83–87]</td>
</tr>
<tr>
<td>Next-generation LLINs</td>
<td>NO: Resistance-breaking, but same limitations as conventional LLINs.</td>
<td>YES: Certain nets are available now and more are under development.</td>
<td>0–5 years</td>
<td>Current next-generation nets cost 2–3 times as much as standard LLINs; not clear that they completely restore efficacy and improve control in all locations; resistance can still evolve.</td>
<td>[90–93]</td>
</tr>
<tr>
<td>Next-generation IRS</td>
<td>NO: Resistance-breaking, but same limitations as conventional IRS.</td>
<td>YES: Certain new products are available and more are under development.</td>
<td>0–5 years</td>
<td>New IRS products cost more than existing IRS so either more money needs to be made available or fewer houses are sprayed; resistance can still evolve; many countries don’t use IRS.</td>
<td>[94–96]</td>
</tr>
<tr>
<td>Sterile insect technique via irradiation</td>
<td>YES: Targets all females and subsequent offspring; independent of blood feeding or resting behavior; independent of insecticide resistance.</td>
<td>YES/NO: Small-scale field trials with Anopheles arabiensis but not yet applicable to other species.</td>
<td>4–8 years</td>
<td>Fitness costs of irradiation; challenges of mass rearing and sorting of males; mating competition with wild types; dispersal constraints; mixed species complexes; public acceptance.</td>
<td>[10,11]</td>
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Table 1. Illustrative List of Prospective Tools/Approaches for the Control of Adult Malaria Vectors, Outlining Modes of Action, Whether the Tool is ‘Field Ready’, the Estimated Time to Operational Use, and Some of the Remaining Research and Development Challenges.
9-day period. These spray treatments reduced mosquito (An. gambiae s.l.) density by 80% over a period of 10 days compared with a control village, and also caused a significant reduction in the female insemination rate [48]. Other similar studies show equivalent results [43]. As with ATSSBs, further work is required to fully evaluate and optimize the spraying pattern and frequency across a wider range of settings, and to determine cost effectiveness. However, swarm spraying requires little specialist equipment, and all the major African malaria vectors, as well as certain Asian and Latin American species [49], elicit swarming behavior, suggesting considerable potential for the approach. Importantly, swarm sprays target males and pre-blood-fed females, so any impact is independent of the blood feeding and resting behavior that can affect LLINs and IRS [43].
House Entry
Houses are not the only location where malaria transmission occurs, but they remain the most important transmission environment in many endemic areas [50–52]. Even with outdoor biting and transmission, there is evidence that a mosquito is likely to enter a house at some point during its life prior to delivering an infective bite [53]. Accordingly, one complementary vector-control intervention is to modify the house to limit mosquito entry.

Modern houses tend to be more protective against malaria than traditional houses made of natural materials that leave multiple gaps through which mosquitoes can enter [54], and in some settings they offer protection equivalent to LLINs [55]. What constitutes modern housing is context dependent, but generally includes a shift in the type of building materials from thatched roofs to metal, and from mud walls to brick or concrete. Houses might also include finished flooring, ceilings, improved doors, window screening, and closed eaves. All of these changes help to make a house more mosquito-proof and can reduce malaria in the inhabitants [56–59].

None of the standard house modifications require new technology per se, but there is a recent innovation that could add to the impact by combining house improvements with targeted insecticide treatment, effectively turning the house into a lethal lure. Open eaves are an important source of host attractant cues and a key entry point for An. gambiae s.l. in Africa [60,61]. Closing the eaves is, therefore, an important mosquito-prevention measure. Eave tubes are pieces of PVC pipe that can be fitted to partially reopen the eaves. The eave tubes contain an insert comprising insecticide-treated netting that kills mosquitoes as they attempt to enter the house through the tubes [62,63]. An electrostatic coating on the insert screening allows for the use of powder formulations of insecticides, a delivery method that is highly effective even against resistant mosquitoes [64]. One benefit of the lethal house lure approach is that it is a passive technology that protects everyone sleeping in the house (IRS is a household-level intervention but generally does not prevent house entry; LLINs provide personal protection but rarely does everyone in a house use a net). As coverage of eave tubes increases, a community-wide mass action effect is also predicted [65].

Eave tubes require only small quantities of insecticide per house, enabling the use of insecticide products that might be too expensive for use in IRS. Replacement of inserts is also very easy, potentially providing a method for delivering insecticides with rapid turnover that would not be appropriate for IRS or LLINs. Beyond diversifying the active ingredients available for vector control, the flexibility and potential for rapid turnover could provide a real opportunity to implement insecticide-resistance management strategies that use insecticide rotations, mosaics, or mixtures [66]. Other house modifications, such as insecticide-treated eave and window screening [67], or insecticide-treated eave baffles [68], could offer similar opportunities, and increase options for extending the ‘lethal house lure’ approach to a broader array of house types (note, however, that eave baffles are designed to allow mosquitoes to enter the house and so, like IRS, do not necessarily provide direct protection against biting). The cost effectiveness of any of these approaches requires further research, and will likely depend strongly on the nature of the local housing. However, leveraging private and public investment in housing improvement could provide a means to improve public health without adding burden to existing public health budgets.

Targeting Livestock
Certain key malaria vectors are strongly anthropophilic. However, there are many vector species or populations that exhibit more diverse behavior, feeding on livestock (zoophilic behavior) as well as on humans. While feeds on nonhuman hosts represent ‘wasted bites’ in terms of acquiring or passing on the malaria parasite, they allow the mosquito to escape the
effects of interventions, like IRS and LLINs, that center on the human host. Targeting these mosquitoes with livestock-based interventions could play an important role in reducing residual transmission [7,8,69].

Mosquitoes feeding on livestock could be targeted through treatment of livestock structures (e.g., IRS of cattle sheds). This approach is attractive as the technology exists, livestock structures tend to be less numerous than households (e.g., [70]), and many of the challenges that apply to conventional IRS (such as inconvenience of householders having to be available to grant access and remove furniture, concerns over odors or staining of walls, etc.) are less relevant [7]. In addition, it might well be possible to use different chemical products than those approved for use in domestic dwellings, providing opportunities for resistance management [7]. Where structures do not exist, livestock-baited tents [71,72] and the use of LLIN fences as livestock enclosures [73] have been shown to kill mosquitoes and reduce mosquito numbers indoors.

Direct treatment of cattle with insecticides by dipping, sponging, or spraying has also been shown to kill mosquitoes [74,75] and to reduce malaria in the human population [76]. One of the challenges in this approach is that many of the candidate insecticides are pyrethroid-based [72,77], and the pyrethroid resistance in Anopheles populations is particularly widespread in Africa. An alternative is the use of systemic veterinary insecticides (referred to as endectocides) that affect the mosquitoes upon blood feeding. Ivermectin has been successfully tested in cattle and demonstrated to kill mosquitoes and shorten the lifespan of survivors [78,79]. Other candidate endectocides are also being explored [80,81], as well as slow-release formulations that could reduce the frequency of retreatment [82].

Spatial Repellents
Spatial repellents (i.e., airborne chemicals that reduce human–vector contact by eliciting one or more changes in insect behavior) have been researched for many years and shown to have potential to reduce transmission (see [83] for overview), including randomized controlled trials demonstrating epidemiological impact of commercially available products [84,85]. A feature of spatial repellents is that they can potentially provide protection in the evening before householders go to sleep and so could be complementary to LLINs [84]. They might also be utilized where LLIN or IRS use is minimal [86]. One of the operational challenges, and the subject of ongoing research, is the development of long-lasting formulations or delivery systems to increase user acceptance and cost-effectiveness [83,87]. However, the use of available consumer products (coils, vaporizers, impregnated mats, etc.) has been correlated with lower risk of malaria at the household level, depending on transmission environment and socioeconomic status [86]. As such, these tools already appear to be contributing, albeit with little strategic integration into control programs.

Concluding Remarks
Increasing the coverage and overall effectiveness of vector control is key to achieving the targets of the WHO Global Technical Strategy for malaria, and the broader goals of elimination and eradication. The current tools, LLINs and IRS, provide the foundation, and intensifying their use is a priority. To maintain the effectiveness of these core tools moving forward there is a need for novel chemical actives that circumvent insecticide resistance (but see Outstanding Questions). However, to supplement existing vector control, to target behavioral as well as physiological resistance, and to address the challenges of residual transmission, requires supplementary methods that target mosquitoes more broadly. Moreover, in order to avert an anticipated rebound in malaria due to waning natural immunity and potential impacts of insecticide resistance, it is essential that new tools enter into operational use within the next 5 or so years.

Outstanding Questions
How much will emerging pyrethroid resistance reduce the effectiveness of core vector-control tools? Better understanding of the effect size of resistance on malaria transmission would help to define the magnitude of the ‘control gap’ that needs to be filled by supplementary tools.

How do we best combine tools to develop locally effective and sustainable integrated vector management strategies, and how should these integrated strategies be evaluated? Conventional randomized controlled trials are extremely challenging when there are multiple factorial combinations of treatments and when effect sizes become small.

Can regulatory and approval mechanisms be streamlined to facilitate adoption of new tools without compromising necessary data on safety and efficacy? For example, can measurements of entomological impact be used as alternatives to standard epidemiological impacts?
The tools we have highlighted here (ATSBs, swarm sprays, housing improvements, livestock treatments, spatial repellents) are among those that both complement existing control and have the potential to be implemented at scale in the near future. In order to make this a reality, a number of interrelated challenges remain (see Outstanding Questions). First, each of the candidate technologies needs further research to evaluate impact and achieve relevant regulatory approvals. Most crucially, there is a need to demonstrate epidemiological impact, as this is the current gold standard for evaluation. Large-scale epidemiological trials are underway for some tools, but further efforts (and hence funding) are required to build the evidence base. One uncertainty here is what constitutes a sufficient body of evidence given both the urgent need for supplementary tools, and the diversity of malaria transmission ecologies and socioeconomic settings. Once proof of principle has been demonstrated in a single epidemiological trial, it might be better to focus efforts on challenges of implementation, rather than conducting further trials in the hope of satisfying the notion of generality. Second, there is a need for economic evaluation and analysis of factors that influence the potential for scale-up, such as user acceptance, supply chains, and distribution networks, costs, and willingness to pay across different market sectors, etc. Third, there is a need to develop appropriate implementation strategies so that individual technologies can be tailored to local ecological and socioeconomic contexts, and combined into optimum integrated vector management strategies [88]. The emergence of supplementary technologies creates new challenges for operational control. For example, should a particular national malaria control program choose ATSBs, or endectocides, or eave tubes, or is there a benefit in combining all three? Answering such questions empirically through the classical approach of randomized controlled trials is extremely challenging. However, if this is the evidence that is required, such trials will need support. Progress to address these challenges over the next 5 years will maximize the chances that these tools can help to sustain the downward trajectory in malaria burden and provide the platform for the next generation of tools (e.g., transgenic mosquitoes) and approaches (e.g., combined vector, drug, and vaccine strategies) to deliver on the ultimate goals of elimination and eradication.

Author Contributions
All authors contributed to the manuscript.

References


18. Xue, R.-D. et al. (2011) Cytoplasmic cctn is an extracellular insect immune factor which is secreted upon immune challenge and mediates phagocytosis and direct killing of bacteria, and is a Plasmodium antagonist. PLoS Pathog. 11, e1004631


35. Xue, R.-D. et al. (2011) Effect of application rate and persistence of toxic acid sugar baits applied to plants for control of Aedes Albopictus. J. Am. Mosq. Control Assoc. 27, 56–60


38. Qualis, W.A. et al. (2015) Indoor use of attractive toxic sugar bait (ATSB) to effectively control malaria vectors in Mali, West Africa. Malar. J. 14, 301


53. Killeen, G.F. et al. (2016) Most outdoor malaria transmission by behaviourally-resistant Anopheles arabiensis is mediated by mosquitoes that have previously been inside houses. Malar. J. 15, 225


71. St Laurent, B. et al. (2016) Cow-baited tents are highly effective in sampling diverse Anopheles malaria vectors in Cambodia. Malar. J. 15, 440
80. Lozano-Fuentes, S. et al. (2016) Evaluation of a topical formulation of ivermectin against Anophelines in karstic habitats when administered to Zebu cattle (Bos indicus) under field conditions. Malar. J. 15, 324
84. Hill, N. et al. (2014) A household randomized, controlled trial of the efficacy of 0.03% transfluthrin coats alone and in combination with long-lasting insecticidal nets on the incidence of Plasmodium falciparum and Plasmodium vivax in western Yunnan Province, China. Malar. J. 13, 208