HHS Public Access
Author manuscript
Trends Parasitol. Author manuscript; available in PMC 2018 October 01.

Published in final edited form as:
Trends Parasitol. 2017 October ; 33(10): 763–774. doi:10.1016/j.pt.2017.06.003.

Priorities for broadening the malaria vector control tool kit

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Abstract

Long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS) have contributed substantially to reductions in the burden of malaria in the last 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.

Keywords

Malaria; vector control; *Anopheles*; insecticide resistance; behaviour; Integrated Vector Management

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 to reduce malaria transmission by at least 90% over the next 15 years, and prevent 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 last 15

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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 insecticide class used on a wide scale on bed nets and 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 nighttime [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 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 President’s Malaria Initiative highlighted examples of 12 broad technologies/approaches for new interventions, including new types of LLINs with resistance breaking properties (http://www.vector-works.org/wp-content/uploads/Vector-Control-Landscape-2015.pdf). Another recent analysis evaluated the evidence for 21 existing and emerging vector control tools excluding LLINs and IRS (http://www.rollbackmalaria.org/files/files/working-groups/VCWG/New challenges%2C new tools in vector control/2_Allison Tatarsky.pdf). 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 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 Foundation (https://www.mmv.org/newsroom/publications/aspiration-action-what-will-it-take-end-malaria), which calls for a halving in transmission every 10 years, leading to ultimate eradication by 2040. Inter-country alliances, such as the Asian Pacific Malaria Elimination Network, aim for regional elimination by 2030 (http://aplma.org/upload/resource/files/APLMA_Roadmap_final_EAS_2015.pdf).

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 chemo-prevention 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 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 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 fails 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 (see 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 transinfection 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 lab-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.

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 extra-floral 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 2–3 days. Resting can take place indoors or outdoors, again depending 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 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 these mosquito activities and the locations in which they take place provide opportunities for disrupting the adult mosquito life cycle and hence, reducing transmission. LLINs and IRS work by lowering 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 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 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 only impact females. Supplementary tools that target adult mosquitoes more broadly at multiple points across their life cycle are needed 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 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). We discuss a number of tools/approaches that we feel have greatest immediate utility in more detail below.

Sugar Feeding

Attractive toxic sugar baits (ATSBs), which utilize a mix 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, indoor bait stations, or can be sprayed directly onto non flowering 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 males 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; 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** (EIR) 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 to 3m 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 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 female insemination rate [48]. Other similar studies show equivalent results [43]. As with ATSB, 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], illicit 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 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 thatch 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 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 and 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 re-open 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 use of insecticide products that might be too expensive for use in IRS. Replacement of inserts is also very easy, potentially providing a method to deliver 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 humans. While feeds on non-human 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 don't exist, livestock-baited tents [71,72] and 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 wide spread 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 both kill mosquitoes and shorten lifespan of survivors [78,79]. Other candidate endectocides are also being explored [80,81], as well as slow release formulations that could reduce frequency of retreatment [82].

Spatial repellents

Spatial repellents (i.e. an airborne chemical that reduces 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 subject of ongoing research, is development of long lasting formulations or delivery systems to increase user acceptance and cost-effectiveness [83,87]. However, 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 socio-economic 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 box]. However, to supplement existing vector control, target behavioral as well as physiological resistance, and 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.

The tools we have highlighted here (ATSB, 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 box]. 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 socio-economic 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 combing 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 supporting. Progress to address these challenges over the next 5 years will maximize the chances that these tools can help 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.

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 are protected directly by an intervention. It occurs, for example, when an intervention kills the mosquito and so reduces the vector-human contact for the whole community

Entomological inoculation rates (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 per 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

Integrated Vector Management (IVM)
the optimal use of diverse tools, tactics, and resources to reduce transmission of disease by vectors

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

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 parasite as it develops, and pass the parasite on to a susceptible host in a later blood meal)

Zoophilic
a preference for feeding on non-human hosts (such as cattle) and potentially resting in and around livestock structures such as cattle sheds

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Trend box

- The last decade has seen a dramatic decline in the burden of malaria, with vector control playing a central role. The aim is now to build on this recent success and progress towards elimination.
- Current core vector controls tools alone are insufficient to achieve this goal, as they fail to target all adult mosquitoes and emerging insecticide resistance is their effectiveness.
- By considering the full range of adult mosquito behaviors, a number of supplementary tools are now under development that complement the core tools and create opportunities for tackling resistance and improving overall control.

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Outstanding Questions Box

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

How good does a novel control tool need to be in order to justify implementation? Determining the value of a technology not only depends on local ecology and socio-economic context but also becomes increasingly complex when multiple tools are deployed together. Integrated strategies might well deliver better overall control but it is almost inevitable that there will be some redundancy between 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 we leverage mechanisms outside the traditional public health sector (such as consumer products and housing improvement) to promote technologies and help bridge funding shortfalls for malaria control?

Can regulatory and approval mechanisms be streamlined to facilitate adoption of new tools without compromising necessary data on safety and efficacy?

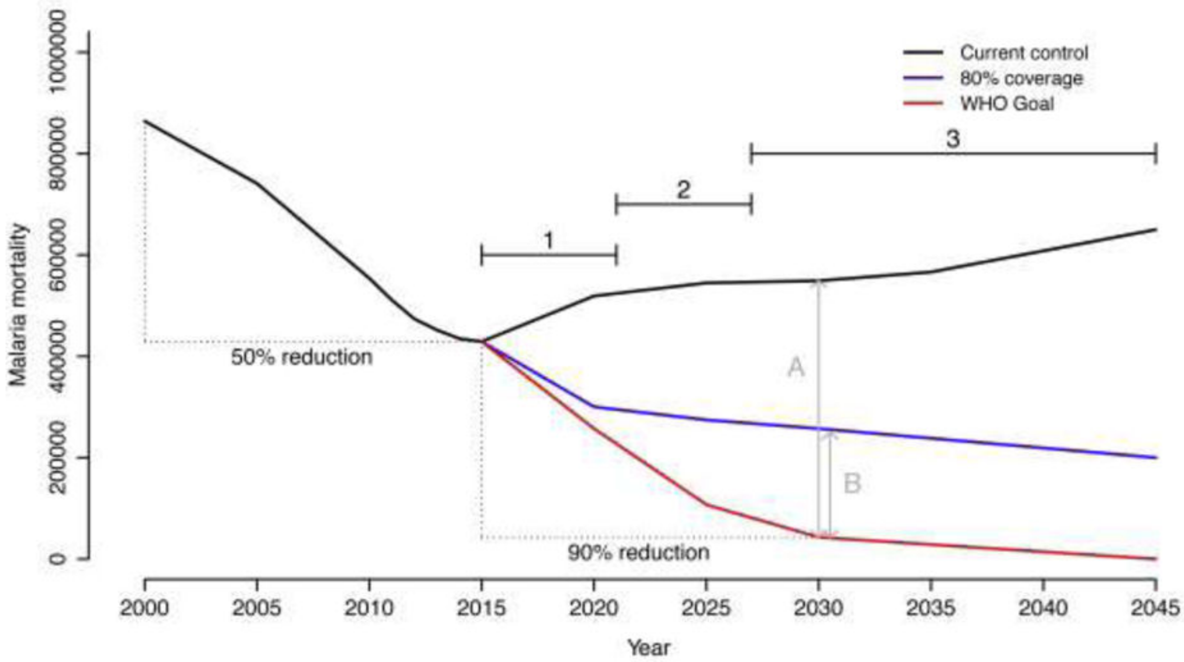

Figure 1. Estimate of historic and projected global deaths due to malaria based on different control scenarios

The figure (modified from [9]) shows estimates of global malaria deaths from 2000–2045. The 50% decline in malaria related mortality recorded from 2000–2015 is largely attributable to the wide scale implementation of vector control tools (Long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS)) [1,2]. The future projections are based on a model analysis that considers different scenarios of access to vector control, together with malaria drug treatments [9].

The graph is modified from Figure 1B of Griffin et al. [9] by using data from the 2016 World Malaria Report [89] to convert the original y-axis of ‘deaths per 1000 people per year’ into estimates of overall malaria mortality per year, and adding the target line for future decline in malaria deaths from the WHO Global Technical Strategy. The back line indicates resurgence in malaria deaths if control efforts remain at current levels. The blue line is the predicted decline in deaths assuming coverage of current control tools can be increased to reach 80% of the population at risk. The red line represents the target set out in the WHO Global Technical Strategy [1], which aims for a 90% decline in malaria deaths by 2030 and then ultimate elimination thereafter.

The arrows A and B illustrate the differences between the WHO target and the two control scenarios. Business as usual clearly represents a massive failure (A). Perhaps more notably, even substantial intensification of existing tools still yields a substantial shortfall (B). These gaps in control demonstrate the need for new interventions. The numbered horizontal lines refer to the estimated timelines for implementation of a range of prospective control tools where: (1) refers to tools that are close to field ready (e.g. attractive toxic sugar baits, housing improvement, livestock targets, next generation LLINs and IRS); (2) represents tools that require a few more years for product development (e.g. improved topical repellents, long lasting endectocides for human use); and (3) tools that either for technical and/or regulatory reasons are still far from operational use (e.g. transinfection with *Wolbachia*, population replacement strategies using genetically modified mosquitoes and gene drive). The fact that the WHO target shows an immediate deviation from the two control scenarios highlights a critical role for tools that can be implemented in the short- and medium-term (1 and 2).

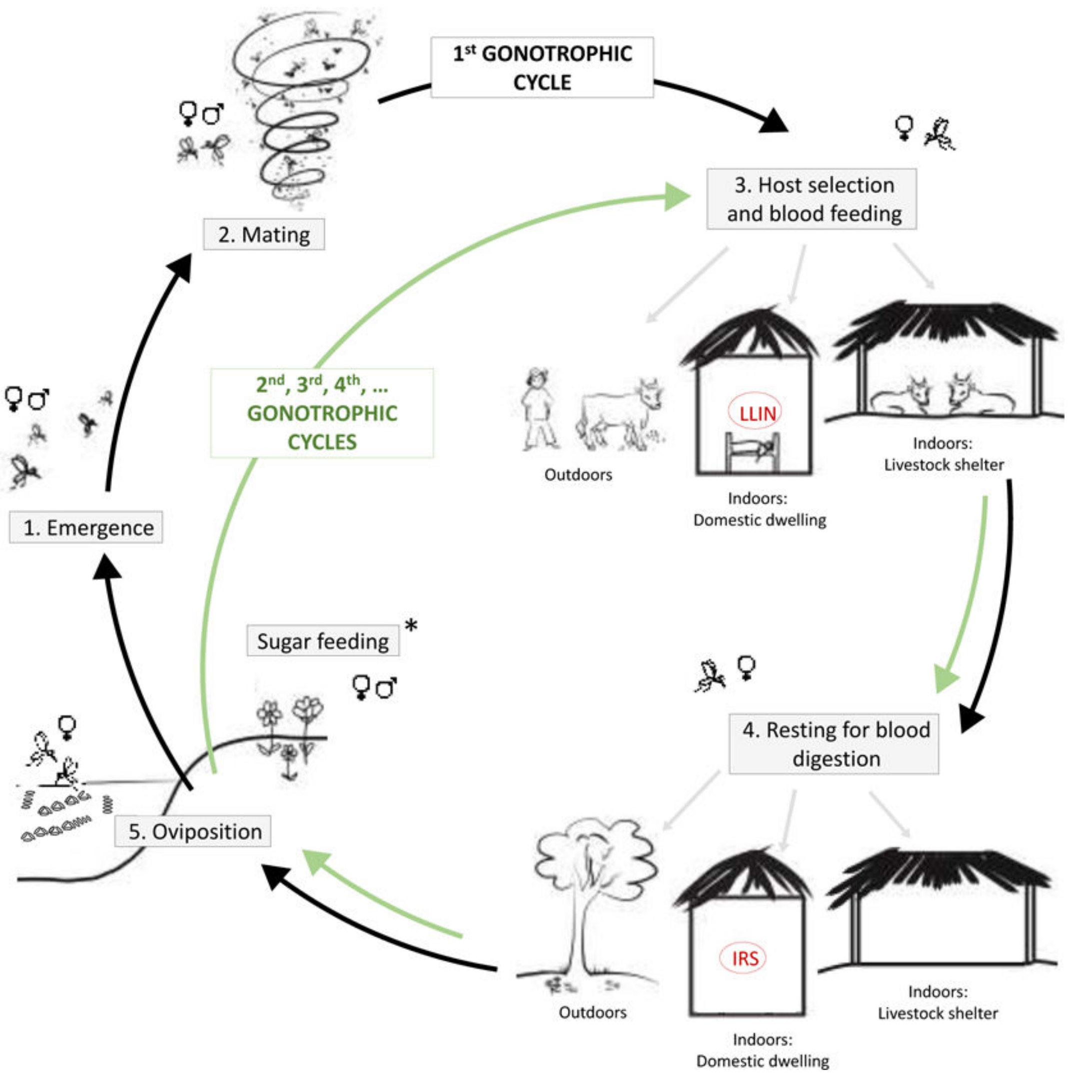

Figure 2. Diverse behaviors and activities of adult malaria mosquitoes as they progress from emergence through to egg laying over one or more gonotrophic cycles

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.

Table 1

Illustrative list of prospective tools/approaches for control of adult malaria vectors, outlining modes of action, whether the tool is 'field ready', the estimated to operational use and some of the remaining research and development challenges.

CONTROL TOOL	COMPLEMENTARY MODE OF ACTION	FIELD-READY TECHNOLOGY	ESIMATED TIME TO USE	CHALLENGES	REFERENCES
Attractive Toxic Sugar Bait	YES: Targets both sexes of diverse mosquito species; repeated exposure across life time; independent of blood feeding or resting behavior; resistance breaking actives.	YES: Ongoing small- scale field trials; simple technology with available products.	0–5 years	Short lifespan when used as sprays on vegetation; further work needed to evaluate in different ecological contexts and to optimize within integrated vector management strategies (IVM); non-target evaluation.	[33–42]
Swarm sprays	YES: Targets males and also pre-gravid females; independent of blood feeding or resting behavior; resistance breaking actives.	YES: Ongoing small- scale field trials; simple technology with available products.	0–5 years	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?).	[43–49]
Housing improvement	YES: Prevents house entry and protects users without LLINs; independent of insecticide resistance; potential for resistance breaking actives in Eave Tubes.	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.	0–5 years	Further research required on appropriateness in different socioeconomic settings; need for cost-effectiveness evaluations and exploration of different implementation strategies.	[50–67]
Livestock targets	YES: Addresses problem of zoophilic vectors	YES: IRS of livestock structures can use existing technology; numerous topical insecticides and endectocides on market.	0–5 years	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 socio-economic contexts.	[68–82]
Spatial repellents	YES: Potentially protects users before they go indoors and users without LLINs.	YES: Certain products already commercially available and used.	0–5 years	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.	[83–87]
Next generation LLINs	NO: Resistance breaking but same limitations as conventional LLINs.	YES: Certain nets are available now and more are under development.	0–5 years	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.	[90–93]
Next generation IRS	NO: Resistance breaking but same limitations as conventional IRS.	YES: Certain new products are available and more are under development.	0–5 years	New IRS products cost more than existing IRS so either more money needs to be made available or fewer	[94–96]

CONTROL TOOL	COMPLEMENTARY MODE OF ACTION	FIELD-READY TECHNOLOGY	ESIMATED TIME TO USE	CHALLENGES	REFERENCES
				houses are sprayed; resistance can still evolve; many countries don't use IRS.	
Sterile Insect Technique via irradiation	YES: Targets all females and subsequent offspring; independent of blood feeding or resting behavior; independent of insecticide resistance.	YES/NO: Small-scale field trials with *An. arabiensis* but not yet applicable to other species.	4–8 years	Fitness costs of irradiation; challenges of mass rearing and sorting of males; mating competition with wildtypes; dispersal constraints; mixed species complexes; public acceptance.	[10,11]
Topical repellents	YES: Independent of blood feeding or resting behavior.	YES/NO: Products do exist but little demonstrated protection against malaria infection (both field trials and metaanalysis).	4–8 years	Need clearer efficacy data; costs; short duration products needing repeat application; user acceptance; potential for resistance	[97–99]
Endectocide for humans	YES: Targets mosquitoes whenever they feed on humans, including outdoor biters.	YES/NO: Some products readily available and undergoing fieldtesting but persistence issues possibly limit current utility.	4–8 years	Need for longer lasting formulations; need better understanding of mode of action; need more efficacy data on lethal and sub-lethal effects; safety constraints; public acceptance; safety monitoring.	[78,81,100–102]
Transinfection with *Wolbachia*	YES: Population replacement or suppression approaches work irrespective of blood feeding or resting behavior, and insecticide resistance.	NO: Laboratory proof of principle only.	8–10 years	Development of technology (stable transinfection in only one *Anopheles* species so far); works best with low density populations; potential fitness costs affecting dispersal and mating behaviors; effectiveness across environments; mass rearing; species complexes; environmental and ethical safety; regulation; public acceptance.	[10,11,19,20]
Population suppression strategies via genetic modification	YES: Targets all females and subsequent offspring; independent of blood feeding or resting behavior, and independent of insecticide resistance.	NO: Laboratory proof of principle only.	8–10 years	Development of technology (there is no clear product as yet for malaria vectors); potential fitness costs; effectiveness across environments; challenges of mass rearing; mating competition with wildtypes; dispersal constraints; mixed species complexes; environmental and ethical safety; regulation; public acceptance.	[10–18]
Population replacement strategies using genetically modified mosquitoes and gene drive	YES: Many possible modes of action independent of blood feeding or resting behavior, and independent of insecticide resistance.	NO: Laboratory proof of principle only.	8–10 years	Development of technology (there is no clear product as yet); potential fitness costs; effectiveness across environments; dispersal constraints; mixed species complexes; resistance evolution against transgene or gene drive; environmental and ethical safety; regulation; public acceptance.	[10–18]

Tools highlighted in bold are those that have modes of action that complement current tools (i.e. target different mosquito behaviors or different segments of the mosquito population than conventional LLINs and IRS) and are sufficiently advanced that they could be implemented in the near term (i.e. either are, or are close to being, 'field ready').