Chapter 16

Newer Approaches for Malaria Vector Control and Challenges of Outdoor Transmission

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Abstract

The effective and reliable management of malaria vectors is still a global challenge. Recently, it has been noted that the first vaccine against *Plasmodium falciparum* malaria, RTS,S/AS01 showed only transient protection, particularly in infants, and rapid resistance has been developing to artemisinin-based drugs. Therefore, the control of malaria mosquito vectors according to strategies of integrated vector management (IVM) is receiving emphasis. A rather wide number of novel mosquito control tools have been tested, including attractive toxic sugar baits, eave tubes, nano-synthesized pesticides loaded with microbial- and plant-borne compounds, biocontrol agents with little non-target effects, new adult repellents, oviposition deterrents, and even acoustic larvicides. However, their real-world applications remain limited. Most National Malaria Control Programs in Africa still rely on indoor residual spraying (IRS) and long-lasting insecticidal nets (LLINs) to reduce malaria incidence but generally have insufficient impact on malaria prevalence. Here, we focus on facts, trends, and current challenges in the employment of the above-mentioned vector control tools in the fight against malaria. We emphasize the needs for better vector control tools used in IVM to overcome the challenges posed by outdoor transmission and growing levels of insecticide resistance, which are threatening the efficacy of LLINs and IRS.

Keywords: *Anopheles*, attractive toxic sugar baits, eave tubes, long-lasting insecticidal nets, mosquito insecticide resistance, *Plasmodium falciparum*, *Plasmodium vivax*

1. Introduction

Malaria is a major challenge to public health; it is caused by *Plasmodium* parasites, obligatorily transmitted to humans through the bites of infected female mosquitoes of the genus

Anopheles (Diptera: Culicidae). There are five known species of *Plasmodium* that cause malaria in humans, *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae* and *P. knowlesi* [1–5]. Currently, 91 countries are endemic for malaria [6]. However, the African region is the most affected with 90% of the cases and 92% of deaths [7–9]. Added to that, malaria has a major impact on the economic development of these countries accounting for both direct and indirect medical costs, such as long-term disabilities and decrease in tourism [10–13].

In the past decade, two significant developments for malaria prevention and treatment were achieved. The first was the discovery of artemisinin, a very effective drug against *Plasmodium falciparum*; this molecule has been studied by the Chinese scientist Y. Tu [14–16]. The second was the development of the vaccine against *P. falciparum* (RTS,S/AS01), by GlaxoSmithKline Biologicals, the PATH Malaria Vaccine Initiative, supported by the Bill & Melinda Gates Foundation, and carried out at several African research centers [17, 18]. However, the vaccine only protected transiently the subjects against malaria [19].

Importantly, new drugs and vaccines are needed to achieve further substantial decrease in the prevalence and incidence of malaria globally and address the increasingly resistance of *Plasmodium* to the drugs currently available such as chloroquine and artemisinin [20–22]. More importantly, effective and scientific-driven control strategies for reducing *Anopheles* vector densities remain the gold standard to prevent malaria transmission [23–25]. However, controlling mosquito populations is a difficult task and is unlikely to be achieved by employing only one tool, such as the use of insecticides commonly employed in the past [26, 27]. Now it is clear that local malaria elimination across different endemic environments will not be achieved with current vector control tools, but will require using several approaches together in the form of integrated vector management (IVM) [28].

2. New tools to fight malaria vectors in an IVM perspective

To decrease the risk of vector-borne disease transmission and increase the effectiveness and sustainability of IVM in reducing mosquito populations, local features should be considered [29]. Therefore, guidelines were developed by the global vector control response (GVCR) including: (1) strengthening inter- and intra-sectoral action and collaboration; (2) enhance vector control surveillance and evaluation of interventions; (3) scale up and integrate tools and approaches; and (4) engage and mobilize communities. The goals of this initiative included increasing the effectiveness of reducing mosquito vectors for both capacity and capability as well as encouraging applied research and innovation [13].

The use of IVM aiming for optimum mosquito control contrasts with strategies used in the past that heavily relied on insecticide spraying. Current mosquito control strategies make use of every available tool. For that reason, regular assessments of local disease transmission dynamics and scientific-driven decision-making criteria are important for achieving effective vector-borne disease transmission reduction [27].

Several tools have been proposed to control vector mosquitoes, especially for the *Anopheles* genus [23, 30]. However, current malaria management programs widely rely on indoor

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residual spraying (IRS), and long-lasting insecticidal nets (LLINs) [5], contrasting with contemporary IVM guidelines. Moreover, residual transmission of malaria has been commonly found using both IRS and LLINs mosquito control strategies [31]. The presence of the insecticide can be translated as a powerful selective pressure, selecting mosquitoes that are able to avoid contact with it. Key shifts in mosquito behavior such as seeking for human hosts outdoors, avoiding contact with LLINs, and finding resting places outside houses decrease the effectiveness of long-lasting insecticidal strategies [32, 33]. The efficacy of LLINs and IRS can be increased if used together with new tools and guidelines available for controlling mosquito populations, as recommended by the Vector Control Advisory Group (VCAG). Some environments are also suited for using *Bacillus thuringiensis* serovar. *israelensis* (Bti) to manage breeding sites [34–38]. Moreover, promising new tools for mosquito control are being developed, the most notable being "eave tubes" and attractive toxic sugar baits (ATSB).

Rural houses in African countries often are constructed with a gap between the walls and the roof to improve ventilation. *Anopheles* mosquitoes usually enter the houses exploiting this architectural structure exposing the residents to infective bites [39]. The "eave tubes" technology comprises the use of plastic tubes with adulticide-coated mesh under the roofline and the installation of a screen to close the remaining gap (**Figure 1**). When mosquitoes try to enter the house through the eaves, they come in contact with the insecticide and die. This technique is based on the attractive power that the human residents represent for the *Anopheles* mosquitoes comprising an "attract and kill" strategy (**Figure 2**) [40, 41]. The ATSB method is also found under the same strategy of "lure and kill"; it exploits the instinct of mosquitoes, both males and females to seek and feed on sugar sources [42, 43]. The ATBS can be deployed in bait stations or sprayed on plants and are co-formulated with low-risk toxic substances, such as boric acid [44–50]. Even though more studies and epidemiological field trials are required, "eaves tubes" and ATSB methods are leading new technologies for vector control that are highly effective, target-specific, and with minimal nontarget effects and contamination of the environment.

Several other modern strategies exploiting different approaches are being developed, including the use of cytoplasmic incompatibility caused by *Wolbachia* endosymbiotic bacteria. This

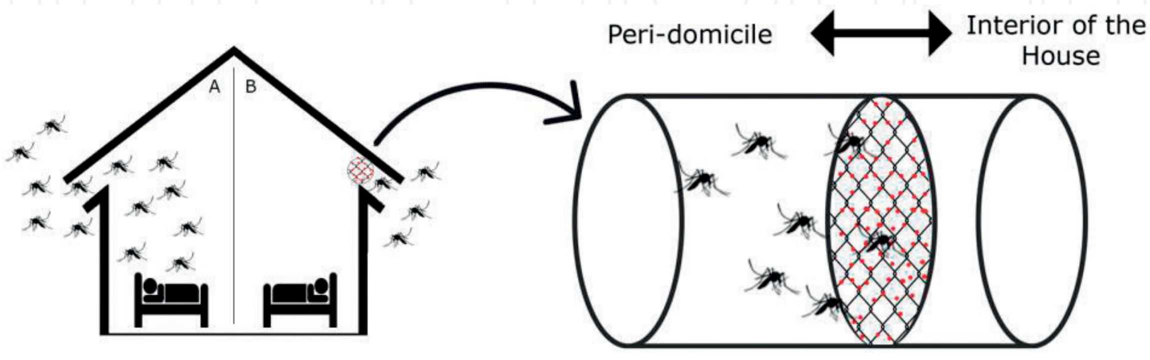

Figure 1. The "eave tubes" technology comprises the use of plastic tubes with adulticide-coated mesh under the roofline and the installation of a screen to close the remaining gap. (A) Graphic representation of a house without "eaves tubes" and (B) with "eaves tubes".

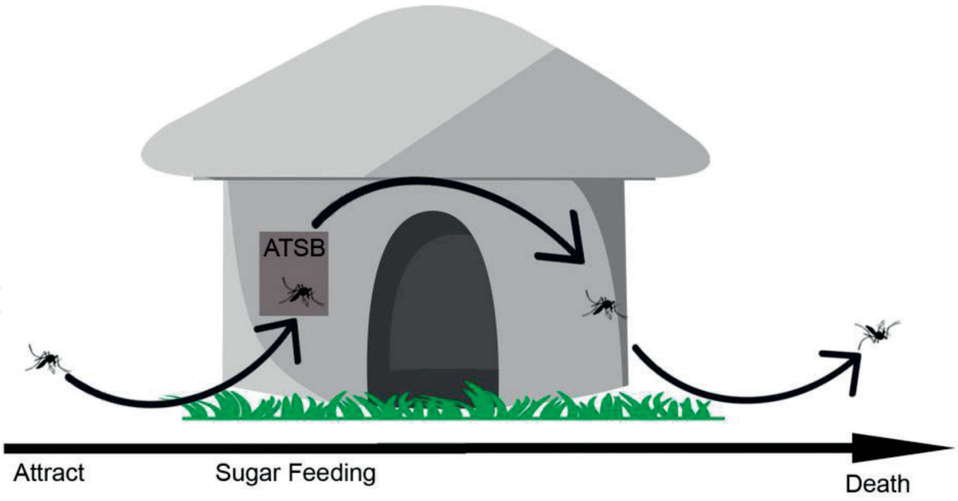

Figure 2. Attractive toxic sugar baits (ATSB) employing an "attract and kill" strategy. This technique consists of using natural attractants such as fruit or flower scent to lure mosquitoes to sugar feeding in a solution containing toxic substances that will lead to its death.

technique has been used to control *Aedes aegypti* and has achieved promising results [51]. Currently, it is undergoing field testing in Brazil and Colombia; however, further studies are needed to transfer this technology to other mosquito species since there are inherent risks for the release of mosquitoes infected with *Wolbachia*, and the result should be monitored for undesirable effects such as increased levels of West Nile virus infection observed in *Culex tarsalis* mosquitoes [52–54]. Other species of bacteria such as *Enterobacter* Esp_Z and *Chromobacterium Csp_P* have been used to inhibit the development of *Plasmodium* in mosquitoes such as *Anopheles stephensi* [55], by increasing the mosquito immune response to *Plasmodium* parasites [31, 56].

The release of irradiated sterile male mosquitoes that will seek and mate with wild females impairing the production of offspring (SIT) is once more being considered as a promising tool for controlling mosquitoes. However, its effectiveness is likely to be decreased by the presence of cryptic species and the presence of multiple *Anopheles* vectors. The same issue should be considered with the use of genetically modified mosquitoes carrying a lethal gene (RIDL), since this technique is species specific and may not be indicated to control outdoor malaria transmission. Genetically modified mosquito techniques based on impairing the *Plasmodium* life cycle inside the mosquito is still in preliminary phases of development and is not likely to be available in the near future [30, 57–61].

The above strategies can be used in the IVM context along with well-established control tools, such as selective microbial and plant-borne pesticides effective against immature mosquitoes, oviposition deterrents, insecticide-coated clothes and other surfaces for personal protection, spatial repellents reducing human-vector contact such as microencapsuled insecticide paint formulation, as well as synthetic and plant-borne repellents [23, 62–69].

The development of plant-based larvicides is of particular interest, and several plant species were successfully used for the synthesis of nano-mosquitocides; nonetheless, plant-based ovicidal and ovideterrent products are still scarce. This technology can provide rapid synthesis of toxic substances and mosquito repellents useful to manage mosquito populations, with minimal toxicity to humans. Even though mosquito control strategies relying on plant-based larvicides are a fast-growing research area, it is still in the preliminary phase of development and several steps should be taken into account, that is, (1) development, characterization, and optimization of potential botanical components suitable for nano-biosynthesis; (2) identification of potential toxic nanoparticles; (3) feasibility of utilization of plant-based industrial by-products as nano-mosquitocides; (4) field evaluation of the effectiveness of plant-based nanoparticles to control mosquito populations; and (5) effect of plant-based nanoparticles on non-target species and environment [70, 71].

Natural predators also have been used to control immature mosquitoes including cyclopoid copepods, *Toxorhynchites* mosquitoes, water bugs, backswimmers, tadpoles, and fishes [72–74]. The efficacy of mosquito predators may vary accordingly to different environmental settings and their impact on non-target aquatic species and difficulty in using multiple or artificial breeding containers should be considered for their use in control strategies [71, 75]. Another approach for controlling mosquitoes is based on endectocide ivermectin, a molecule that has been used for more than 30 years to control lymphatic filariasis. This molecule remains in the human bloodstream following a standard oral dose and can kill *Anopheles* mosquitoes that feed on the blood of medicated persons [76–79]. Controlling vector mosquito populations is a difficult task and so the addition of new technologies to be considered for IVM will help improve the effectiveness of vector-borne disease transmission [80–83].

Current strategies for malaria vector control used in most African countries still rely on LLINs and IRS, which generally are not sufficient to achieve successful malaria control and local elimination [13, 25, 84]. Even though LLINs and IRS are very effective for in-house reduction of malaria transmission, in endemic areas, it has been showed that insecticide-treated bed nets reduce malaria prevalence only by 13% [85–91]. Furthermore, due to the high abundance of mosquitoes, even low levels of *Plasmodium* transmission undermine efforts to reduce the prevalence of malaria, since human hosts are bitten multiple times increasing the chance of coming in contact with the parasite. The prevalence of *P. falciparum* is strongly related to the number of infective bites per person per year or annual entomological inoculation rates (EIRs), ranging from <1 to >500. Malaria prevalence is positively associated with high EIRs; however, even low annual EIRs (<5) can be associated with malaria prevalence levels of 40–60%. For a significant reduction in the prevalence of malaria, EIRs must be lower than 1 [92]. Vector control strategies implemented in Africa have so far been unable to achieve such low levels of malaria transmission [93].

Besides, with the increase in the control efforts focused into indoor mosquitoes, the dynamics of malaria transmission is shifting from the highly endophilic to more exophilic outdoor-adapted species within the *Anopheles gambiae* complex [94–99]. In Asia, the main malaria vectors of the *Anopheles dirus* complex are exophagic and difficult to target with conventional control strategies [31]. Moreover, increasing resistance to insecticides renders LLINs and IRS less effective for controlling *Anopheles* populations. As well, even though larvicides are effective against immature mosquitoes, they are not recommended for application in rural areas [100–105].

3. Conclusions and issues to watch for

The importance of basic knowledge on mosquito vector behavior and ecology for the development of tailor-made vector control strategies is considered key in the recent WHO Health and Environment Linkages Initiative (HELI), highlighting its importance for sustainable long-term mosquito control actions [106–111].

Recently, an updated research agenda for malaria elimination and eradication (malERA) was published [26, 112–114]. It comprises a multidisciplinary approach to the most important challenges of controlling malaria. Several factors significantly impact the dynamics of malaria transmission. Specifically, shifts in mosquito ecology and behavior caused by anthropogenic alterations in the environment have a major impact on the effectiveness of control strategies. These alterations include, but not limited to, urbanization, human movement, availability of breeding containers and water bodies, hosts for blood feeding and availability of sugar sources and resting places. Moreover, mosquito insecticide resistance, behavioral avoidance, high vector biodiversity, competitive and food web interactions, mosquito population dynamics and dispersion also play a major role in the complex scenario comprising the dynamics of malaria transmission [17, 115, 116].

The development of reliable and effective mosquito control strategies is no easy task, and several challenges must be overcome to achieve a long-term sustainable reduction of mosquito populations. Most of the new strategies and tools developed for controlling vector mosquito populations are not rigorously tested, and most of the time, their real epidemiological impact is not properly assessed rendering the deployment of ineffective mosquito control strategies with limited result on the prevalence of vector-borne diseases [117]. These challenges can be classified as systemic, structural, informational, environmental, human movement, political and financial ones [13]. Key core issues have to be addressed in order to decrease the prevalence of malaria, such as (1) vector surveillance is often neglected or insufficient in most countries at risk of mosquito-borne diseases, rendering control efforts ineffective; (2) malaria endemic countries are often endemic for more than one major mosquito-borne disease depleting the availability of resources; (3) there is a lack of scientific evidence to guide the efforts for mosquito control; (4) anthropogenic alterations in the environment and global warming are responsible for driving the abundance of vector mosquitoes, directly affecting the effectiveness of control strategies; (5) the increase in the human population and movement of people is associated with the dispersion of vector mosquitoes, exposing non-immune populations to new diseases; and (6) funds for vector surveillance are negligible and even though financial support has been made available for LLINs and IRS for controlling *Anopheles* mosquitoes, other vector-borne diseases are largely neglected [13, 17, 118, 119].

Priorities in vector control should be defined by the national vector-borne disease control program and studies designed and performed in consultation with national and international experts in the relevant field. The plan should consider a list of strategic key areas necessary to implement vector control in a given country, followed by research guidance from academic institutes and companies [27]. The most important topics to be considered that are also in agreement with the WHO criteria, comprise: (1) assessment of the health system limitations to improve processes and methods aiming for the improvement in efficacy of vector control; (2) implementation

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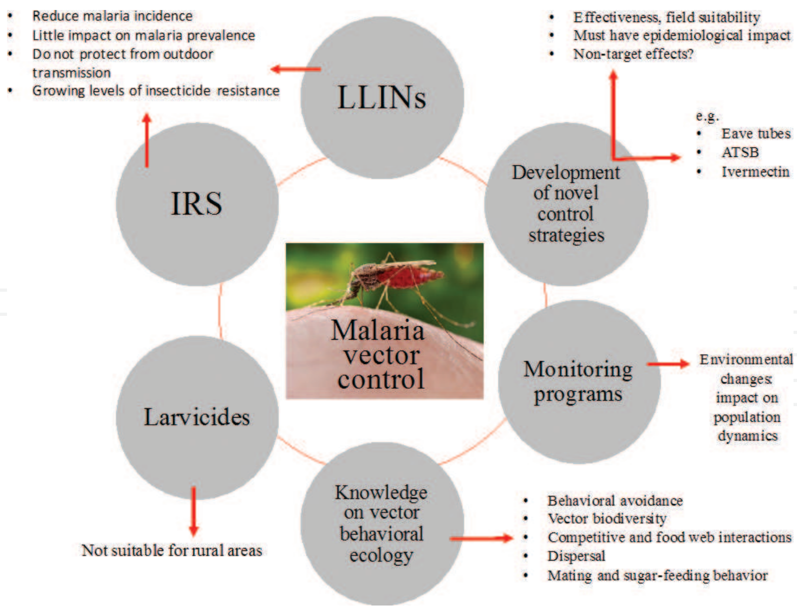

Figure 3. Main challenges and trends in current malaria vector control research (adapted and modified from [120]).

of mosquito surveillance for the development of guidelines and models of the risk of disease transmission (**Figure 3**); (3) development of effective and environmentally friendly strategies to reduce malaria and other vector-borne disease transmission, following the recommendations by VCAG and considering the increase of insecticide resistance [100, 102]. To our understanding, traditional insecticide-based control efforts, such as IRS and LLIN, should be used in combination with novel eco-friendly tools, such as "eave tubes technology," ATSB methods, and even the employment of the ectendocide ivermectin [40, 44, 76]. These new mosquito control tools should be accompanied by (4) an evaluation of their effectiveness, assessment of their usefulness and impact through randomized controlled trials with entomological and epidemiological outcomes (**Figure 3**), this has been done for traditional control strategies such as LLINs and IRS; (5) the monitoring of man-made alteration in the environment and its impact in the dynamics of malaria vectors; and (6) the establishment of a multi-disciplinary team with different areas of expertise (**Figure 3**) [100, 102, 120]. Indeed, the transdisciplinary cooperation among professionals is important for ensuring adequate evaluation of the epidemiological impact triggered by novel mosquito vector control strategies.

Here we illustrate the complex scenario comprising the epidemiology of malaria and how anthropogenic selective pressures are modulating the ecology and behavior of vector mosquitoes. To our understanding, there is no other choice rather to use rigorous, science-driven strategies for controlling vector mosquito populations.

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