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The untapped potential of mosquito lures for malaria vector surveillance and mass trapping of mosquitoes: A review

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Abstract

The expansion of vector borne diseases is occurring at a time when unprecedented discoveries are being made in vector biology specifically in areas of genetics, genomics, and physiology. Among the many new discoveries in mosquito physiology is the use of chemo-attractants for mosquito surveillance and mass trapping; which are increasingly being used despite the fact that they're still limited to small scale field and semi-field trials in most parts of the world. Once malaria vector surveillance is fully achieved, it is our hope that it will boost the preparedness of health systems using data derived from assessment of the introduction, establishment and spread of the vectors. However, this comes at a time when parts of Africa and Asia are battling with the resource capacity inadequacy in terms of medical entomologists. This paper therefore presents the use of mosquito lures as an example of the many new interventions that researchers are exploring to address one of the important global health challenges, of eliminating malaria by 2030. It's at a glance when the insecticidal based methods are increasingly becoming insufficient to control the spread of malaria and other vector borne diseases especially in the endemic countries of sub-Saharan Africa.

Keywords: Efficacy, mosquito lures, chemo-attractants, odorants, baits, mass trapping, malaria

1. Introduction

The spread and resurgence of vector-borne diseases remains a global public health concern requiring prompt and effective response measures ^[1]. Vector borne diseases, as a specific group of a (re-)emerging infections, are increasingly posing a threat to public health and therefore, require particular attention and new strategies in combating them ^[2, 3]. They also represent a great proportion of the neglected tropical diseases (NTDs) in tropical regions of the world, where they disproportionately affect the poorest and most disadvantaged populations, with the greatest killer of them all being malaria ^[4]. The World malaria report 2018 estimates that there were 219 million cases of malaria in 2017 alone ^[5]. The 10 highest burden African countries saw an estimated 3.5 million more malaria cases in 2017 compared with the previous year ^[5]. Malaria continues to claim the lives of more than 435 000 people each year, largely in Africa with the most vulnerable being children under the age of 5 ^[5]. In 2010, deaths from malaria in Nigeria were the highest recorded worldwide ^[6]. The key to contemporary management of vector borne diseases like malaria, dengue, yellow fever, Zika virus and lymphatic filariasis is control of the insect vectors responsible for disease transmission ^[7]. The advance in the fight against malaria is largely due to the mass distribution of treated mosquito nets, especially the long lasting insecticide nets ^[6]. Insecticide-based interventions have contributed to declines in disease burdens in many areas, but this progress has been threatened by the emergence of insecticide resistance in vector populations ^[7]. Researchers are now exploring new approaches such as the push-pull strategy; designed either to repel host-seeking mosquitoes from houses and their immediate surroundings (the "push") or to lure them towards odor-baited mosquito traps (the "pull"), which are placed outside the home ^[8]. Push-pull strategies involve the behavioral manipulation of insect vectors and their natural enemies via the integration of stimuli that act to make the protected resource unattractive or unsuitable to the pests (push) while luring them toward an attractive source (pull) from where they are subsequently removed after being trapped ^[8]. These methods can be integrated with other biological control methods since they are non-toxic ^[8].

The pulling component (chemo-attraction) mainly relies on the complexity of the olfactory system of mosquitoes but if used properly, it can reduce the spread of malaria parasite, *Plasmodium falciparum* [9, 10]. Recent progress in molecular and computational tools has enabled rigorous investigations of olfaction in mosquitoes, specifically the role of receptors towards attractive and aversive behaviors [11, 1]. Mosquitoes rely on biochemical cues to find essential resources such as human hosts, mates and suitable sites to lay their eggs [12, 13]. African mosquitoes *Anopheles gambiae* sensu stricto and *Anopheles funestus* for example, are efficient vectors of human malaria because they are highly adapted to preferentially feed on humans [14, 15]. Using their highly sensitive olfactory organs, these mosquitoes can select more attractive persons over less attractive ones by identifying chemicals present in breath, sweat and other skin emanations originating from the persons [16, 17]. Though not adequately understood, these evolutionary host preferences may benefit the mosquitoes in a number of ways including the identification of hosts with more nutritive blood, or those who are less defensive against mosquito bites [18]. Examples of these attractive chemical substances include carbon dioxide (CO₂), the ultimate catabolite of vertebrate respiratory processes, L-lactic acid, which is produced through anaerobic glycolysis in human exocrine glands, ammonia, carboxylic acids and several alkenes which are also components of human sweat [14, 19]. Many of these odorants can be naturally obtained from plant extracts (mostly alkenes), fungi, among others but majority of them can be synthesized in vitro and therefore they can be reformulated to produce mixtures that mimic real humans to lure mosquitoes on a large scale [20, 21]. While some synthetic odor mixtures already exist which can lure host-seeking mosquitoes, evidence supporting their utility is largely limited to short range evaluations inside laboratories, where the crucial role of long-range stimuli is artificially negated [23, 22]. These chemicals enhance the catch rate by acting along with the CO₂ neuronal circuit in the nervous system [24, 11]. Recent molecular approaches have gone further in identifying specific vector-plant associations, which can be exploited in maximizing control strategies such as attractive toxic sugar bait and odor-bait technology [1].

2. Mosquito cues and lures

Host-seeking mosquitoes rely on a range of sensory cues to find and approach blood hosts, as well as to avoid host detection [25]. By using odor blends and visual cues that attract anthropophilic mosquitoes, odor-baited traps have been developed to monitor and control human pathogen-transmitting vectors [25]. Female mosquitoes are activated, attracted, and oriented to a potential blood meal host via response to various cues [26]. Host seeking behaviors are complex, involving multiple systems that respond to two major cues; physical and chemical [26]. The stimuli used by mosquitoes such as vision, hearing, and chemo-reception to detect hosts can be categorized as short or long-range cues [17]. Long-range cues include visual and olfactory signals, whereas short-range cues include visual, olfaction, temperature, and sound [17]. These physical cues include visual cues of the landscape and vegetation, as well as contrast motion and color [26]. Physical cues also include heat and humidity which are detected using their thermo-receptors within sensilla on their antennae [26]. Host chemical cues encompass all the volatile stimuli released into the atmosphere by the host that

mosquitoes respond to, resulting in a behavioral response [26]. These include but are not limited to carbon dioxide (CO₂), 1-octen-3-ol (octenol), 2-butanone, L-lactic acid (component of sweat), ammonia, alkenes, alcohols and other emissions that hosts release through skin or respiration [27, 28]. Female mosquitoes pick up chemical cues using sensory receptors located on sensilla on the maxillary and labial palps, as well as on the antennae (and probably elsewhere) that are sensitive to these substances in varying concentrations [29, 26]. Several odor bait sources have been investigated including: human foot odor [30, 12, 31], human breath [32] and sheep, goat, pig, cattle [33], monkey odors [34] and plant extracts [35]. Just like CO₂, there is a pair of chemo-receptor neurons sensitive to these substances like L-lactic acid in the grooved-peg sensilla in some mosquitoes [36]. 1-octen-3-ol is detected by OR8 (olfactory receptor 8) in the neuron neighboring the CO₂-sensitive odorant receptor neurons in the same sensillum but with a higher magnitude of sensitivity [24, 11]. Also, ammonia-sensitive olfactory receptor neurons have been observed in grooved-peg sensilla and trichoid sensilla of mosquitoes too [11].

2.1 Carbon dioxide lures

Carbon dioxide (CO₂) has been used for decades to enhance capture of host-seeking mosquitoes when released in association with traps commonly used by mosquito and vector control agencies [37]. CO₂, a gas emitted from all vertebrates in detectable amounts, is known to attract mosquitoes to a potential blood meal host, and is easy to re-create in association with traps using dry ice or CO₂ tanks [15]. Female mosquitoes are sensitive to changes in CO₂ concentrations as low as 0.01% [29]. It should be noted that CO₂ alone is not sufficient to induce a mosquito to enter a trap, hence it is used with the aid of powered fans to suck them in [38]. Traps baited with CO₂ are highly effective attractants for host-seeking female mosquitoes [2]. The commonly used CO₂ baited traps include: CDC light traps, gravid traps, BG-Sentinel and Biogents Mosquitair traps and Mosquito magnets [2]. Normally they are operated with dry ice or a carbon dioxide tank, in such a way that they produce carbon dioxide through sublimation [2]. Despite being simple, robust, portable and not significantly influenced by background light in urbanized areas, these traps need to have access to dry ice or gaseous CO₂ [2]. However, CO₂-baited traps have been widely used in field sampling and mass trapping of mosquitoes but their utilization in mass trapping of mosquitoes is still low [2]. Homan *et al.* (2016) assessed the effects of mass deployment of odor-baited traps on malaria transmission and disease burden. It was discovered that there was a substantial effect on malaria prevalence during the study, explained by reduction in densities of *Anopheles funestus*, one of the major vectors of malaria [39]. A related study by Njiru *et al.* (2006) also indicated the potential of CO₂ in mass trapping of African mosquito vector, *Anopheles gambiae* especially in combination with foot odor [40]. These studies therefore show that mass trapping of mosquitoes using CO₂-baited traps might be an effective malaria intervention [40, 39].

2.2 Attractive toxic sugar lures

Malaria elimination is unlikely to be achieved without the implementation of new vector control interventions capable of complementing insecticide-treated nets and indoor residual spraying [41]. Attractive-toxic sugar baits (ATSBs) are

considered a new vector control paradigm ^[41]. They are technologically appropriate as they are simple and affordable to produce whereas they kill both female and male mosquitoes attracted to sugar feed on a sugary solution containing a mosquitocidal agent and may be used indoors or outdoors ^[41]. In a study by Xue *et al.* (2011), it was suggested that boric acid baits applied to plant surfaces may provide specific data related to the development of an effective point source-based adjunct to the use of conventional adulticides for mosquito control ^[42]. However, the efficacy of attractive toxic sugar baits has been tested on a small scale and on limited mosquito species, for example in some communities in Coastal Tanzania where they have proven to be effective but further investigative trials are needed to confirm their efficacy to lure mosquitoes and consequently reduce malaria ^[41].

2.3 Animal-baited traps

Animal-baited traps use a variety of isolated odors from animals such as cattle, horses, goats, pigs, sheep, rodents and various birds ^[2]. Mosquitoes are attracted by different cues from a number of hosts, and host preferences differ between species ^[2]. For example, *Culex territans* feeds preferably on amphibians, *Culex pipiens* is known to feed on birds, other animals and also on humans; some *Anopheles* species feed on humans and animals ^[2]. *An. arabiensis* has been found to be attracted to cow and chicken odors, which confirms its opportunistic behaviour ^[43]. Busula *et al.* (2015) also showed that baits derived mostly from cows significantly increased catches of *An. arabiensis* and *Culex* species ^[43].

2.4 Synthetic mosquito lures

Recent investigations have established that the catch rates of CO₂ lures can be increased significantly by the addition of synthetic odorants that can act synergistically, often identified from animal skin and plant extracts ^[35, 24, 11]. Examples of known synthetic plant-based mosquito lures include: linalool oxide, linalool oxide, β-ocimene, hexanal, β-pinene, limonene and β-farnesene, β-myrcene ^[35, 11]. Whereas those from animals include carboxylic acid mixtures, lactic acids, ammonia, 1-octen-3-ol, 2-butanone nonanal among others ^[24, 11, 21]. These chemicals also enhance the catch rate by acting along with the CO₂ neuronal circuit in the nervous system ^[24, 11]. Different odor baits elicit varying responses among mosquito species ^[43]. *An. gambiae* for instance is more attracted to sesquiterpenes and alkenes compared to other plant-based lures ^[11]. Nyasembe *et al.* (2014) tested the efficacy of plant-based synthetic odor baits in trapping outdoor populations of malaria vectors ^[35]. It was discovered that plant-based odors have the potential, specifically linalool oxide, with or without CO₂, for surveillance and mass trapping of malaria vectors ^[35]. On the other hand, the synergistic effect of most animal-derived synthetic chemo-attractants is obtained when they are used in combinations, for instance, L-lactic acid combined with ammonia and the carboxylic acids in a mosquito blend ^[44], and seemingly less effective when used alone ^[45, 12]. Therefore, they are often combined with plant extracts and organic substances ^[46, 46]. Thus, the use of plant-produced kairomones and synthetic animal blends has significant promise for the surveillance and integrated control of malaria vector populations in Africa and Asia ^[35].

3. Potential applications of mosquito lures

The search for a standard human surrogate in the form of a synthetic mosquito attractant has been the goal of many laboratories around the world ^[31]. This is because the use of human volunteers as baits in mosquito traps inevitably limits their compactness, consistency, cost and safety, and has restricted the development of sustainable mosquito surveillance systems ^[47]. The mosquito lures that are being explored can substitute for human subjects as baits in mosquito surveillance and limit the possibility of transmission of pathogens to humans ^[12]. Besides alleviating the occupational risk subjected to volunteers participating in vector surveillance and control, discovery of potent attractants underpins the development and deployment of mass trapping devices for controlling mosquito-borne diseases ^[31]. Mass trapping, despite its underlying conceptual, technical, logistical and financial limitations, has been successfully demonstrated for mosquito population reduction in the USA ^[48, 28]. Such mass trapping strategies once adopted in sub-Saharan Africa and Asia where malaria is endemic will simultaneously suppress nuisance bites from harmful Culicine mosquitoes ^[3]. Cook *et al.* (2007) suggested that mosquito lures can be effectively integrated with the existing malaria control tools in a push-pull strategy similar to that commonly practiced in agricultural pest management ^[8]. For example, where people use insecticide treated nets (ITNs) or indoor residual spraying with insecticides (IRS) which apart from being lethal targets also deter mosquitoes from entering houses, odor baited traps could be strategically located so as to trap the mosquitoes deterred from dwellings ^[8]. Mathematical simulations using adaptations of established transmission models suggest that appropriate trap devices baited with these lures could reduce exposure to malaria, and effectively complement ITNs in areas of highly intense malaria transmission in Africa ^[12].

4. Challenges and opportunities

The successful development of odor-baited trapping systems for mosquitoes depends on the identification of behaviorally active semio-chemicals, besides the design and operating principles of such devices ^[40]. A large variety of 'attractants' has been identified in laboratory investigations, yet few of these increase trap catches in the field ^[40]. Recent large-scale epidemiological trials have conclusively demonstrated mass suppression of the notoriously efficient African vector *An. funestus*, and dramatically reduced malaria transmission using odor-baited traps targeting host-seeking mosquitoes ^[39]. The introduction of solar-powered traps which are self-sufficient with surplus power for households is increasing the need to distribute such traps programmatically through horizontal delivery mechanisms as people are slowly taking up the innovation ^[39]. Efficacy against a wider diversity of vector species will, however, require the development of affordable sources of CO₂, or low-bulk substitutes for it ^[39]. Smith *et al.* (2004) suggested the need for optimization of behaviorally active formulations in larger semi-field systems and enhancement of the development of mosquito lures ^[49]. However, the availability of consistent and effective bait for representative sampling of a wide range of host-seeking mosquitoes also means that it should be in position to measure human exposure to mosquito-borne infections yet almost all the synthetic mosquito baits being used to date are much effective outdoors (semi field and field conditions) ^[12]. In

addition, to set up and run the traps for example, experienced technicians or medical entomologists are needed, and when a large number of traps are set up in a large area, several teams might be necessary which of course are still lacking in most

parts of the world [2]. In general, the main bottlenecks that impede the use of mosquito lures in malaria endemic regions are summarized in the table (Table 1) below.

Table 1: Summary of some challenges to the application of mosquito lures

Number	Challenges	Citations
1.	Expensive baits and trapping devices	[50]
2.	Lack of affordable sources of energy to power traps	[39]
3.	Lack of cheaper sources of CO ₂ and other attractants	[51]
4.	Inadequate cheap and easy methods for delivering mosquito synthetic attractants	[52]
5.	Ignorance and illiteracy of communities about these technological advancements	[6, 41]
6.	Low diversity of synthetic attractants	[25]
7.	Some species are difficult to collect with the available adult traps	[2]
8.	Lack of a generic attractant that can trap multiple vectors	[2]

Once all the challenges discussed above and in the table (Table 1) are resolved, eradication of malaria and other mosquito borne infections will be at a glance. In Nigeria, much work still needs to be done to reduce malaria incidence to a minimum level [6]. Since no single individual method has proved to achieve a successful malaria control, strategic control methods must involve some combination of effective clinical control, vector control, reduction in contact of the mosquito with its human host, improved sanitation, and better health education and malaria prevention programs [6]. Global policy must now support the development such an expanded toolbox for vector control right from investment in product and systems development, to high-quality evaluations of efficacy and effectiveness of mosquito baits in mass trapping of mosquitoes and vector surveillance [53]. Strong political will, sustainable and predictable financing, and inter-sectoral collaboration will be crucial for the successful scaling up and integrating of vector control strategies [53].

5. Conclusions

Mosquito lures ideally offer a promising means for mosquito vector surveillance and mass trapping. However, there is still a low utility of odor baited traps in malaria endemic countries to reduce the disease burden. In Nigeria and generally, the sub-Saharan region, it would be worthwhile evaluating their performance and the efficacy of mass trapping in a bid to eliminate mosquito borne diseases. Global policy must now fully and consistently realign with these biological realities of mosquito vector control by prioritizing the accelerated development of these diverse options, towards malaria elimination.

6. Declarations

The authors declare that they have no competing interests.

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