Control Strategies for Mosquito-Borne Diseases

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Mosquito-borne diseases are spread by the bite of infected female mosquitoes. The main mosquito-borne diseases include malaria, Chikungunya, Zika, Dengue, West Nile, yellow fever, Rift Valley fever, *Lymphatic filariasis*, and tick-borne encephalitis. Various chemical, biological, and mechanical methods are used to control mosquito-borne diseases hence reducing their burden.

mosquito control strategies nets

1. Chemical Control Strategies

The chemical methods commonly used for controlling mosquito-borne diseases include long-lasting insecticide-treated nets (LLINs), indoor residual spraying (IRS), peridomestic space spraying, and the use of mosquito repellents among others. These approaches that target the adult stages of the vectors are summarized below.

1.1 Long-Lasting Insecticide-Treated Nets

Long-lasting insecticide-treated nets (LLINs) are factory-made using a fabric treated with an insecticide, usually pyrethroids. Based on unique new fabric technologies and drawbacks associated with the conventional insecticide-treated nets (ITNs), LLINs were invented to withstand repeated washings of up to twenty times under use in field conditions [1]. These LLINs provide physical barriers against host-seeking mosquitoes, and in addition repel or kill the mosquitoes after coming in contact with the chemicals coated on the net fabric [2]. In this way, LLINs offer protection from and control of mosquito-borne diseases both at individual and community levels for a longer duration. Long-lasting insecticide-treated nets are regarded as one of the most effective mosquito control interventions, particularly for preventing malaria [3]. The fact that LLINs do not require retreatment results in lower use of insecticides and consequently a lower emission of the latter into the environment [1][3][4]. The choice of molecules for LLINs relies on whether or not they are effective against the target organism, and proper application may increase their efficacy [2].

In sub-Saharan Africa, where more than 427 million insecticide-treated nets were distributed between 2012 and 2014, morbidity and mortality due to malaria have significantly decreased (by almost 50%) [4]. Long-lasting insecticide-treated nets have also helped to reduce malaria during the past 15 years in pregnant women and children globally [4][5][6][7][8][9]. In a study that was conducted in the southeast of Iran by Soleimani-Ahmadi et al. [9], the prevalence of malaria in groups of LLIN users was dramatically reduced (up to 97%) when compared to groups of LLIN non-users. However, the success of LLINs in averting mosquito-borne diseases depends on several climatic parameters [10]. Access to LLINs also plays a significant role in determining their success [11][12]. Moreover, the effectiveness of LLINs is being hampered by the development of insecticide resistance to the pyrethroids used for their treatment [7]. Hence, there is a need to revamp this vector control tool if mosquito-borne diseases are to be scaled down.

1.2. Indoor Residual Spraying

Indoor residual spraying (IRS) involves spraying insecticides inside houses on surfaces that serve as resting places for mosquitoes [13]. *Ae. aegypti*, which primarily rests indoors and feeds on humans, is usually the most affected endophilic species as it is more likely to be reached by IRS than by space sprays [13]. Indoor residual spraying has some drawbacks and flaws, such as the requirement for specialized training, which takes time. Furthermore, it does not stop people from being bitten by mosquitoes [14].

Indoor residual spraying used alone or in combination with larval control can significantly reduce the population of mosquitoes and the disease prevalence [15][16]. The United States President's Malaria Initiative (PMI) supported the World Health Organization's 2006 affirmation of IRS's significance for reducing malaria transmission in 2012 in the Mediterranean region [17]. Consequently, malaria appears to have dwindled as a result of IRS-based malaria eradication programs [18]. In light of insecticide resistance development to pyrethroids among mosquitoes, alternative formulations, such as bendiocarb, are currently being used in the IRS to prevent vectors from developing insecticide resistance [19][20].

1.3. Peridomestic Space Spraying

Peridomestic space spraying is the pulverization of insecticides (e.g., dichlorodiphenyltrichloroethane (DDT)) around the home. Through dispersing tiny droplets of insecticides into the air, this method targets only adult mosquitoes and has no direct effect on immature stages (egg, larvae, or pupae) [18]. Peridomestic space spraying is mostly employed in emergency situations to reduce the enormous adult mosquito population [20]. One of the most commonly used approaches in peridomestic spraying is the ultralow volume spray which uses a machine that is hand-held or mounted on a vehicle [20]. Depending on the proportion of the active component in the formulation, the insecticide concentration usually ranges from 2% (pyrethroids) to 95% (organophosphates). The concentration of these active ingredients depends on their toxicity to the target species [18]. Pyrethrin aerial spraying has a substantial influence on the non-target organisms but not on the water quality [21]. Since Dengue and Chikungunya viruses can spread to a small extent by trans-ovarian transmission, mosquitoes that emerge after treatment may still be vectors. Therefore, it is important for the breeding ground of Dengue and Chikungunya vectors to receive subsequent treatments, which should be administered at intervals [18].

1.4. Mosquito Repellents

Mosquitoes are primarily drawn to people by the lactic acid and carbon dioxide in their sweat, which their antennae can detect [22]. Mosquito repellents are substances that do not kill mosquitoes but deter them from biting people

[22]. The most commonly used repellents obliterate the human aroma, making them efficient insect repellents [18].

Among the synthetic insect repellents, DEET (N, N-diethyl-m-toluamide or N,N-diethyl-3-methylbenzamide)- and IR3535 (3-(N-Butyl-N-acetyl)-aminopropionic acid)-treated clothing works well as a long-lasting insect-repellent [23]. However, the use of synthetic repellents has generated a lot of criticism since it makes mosquitoes resistant to insecticides, harms organisms that are not the intended targets, and poses a threat to the ecosystem [23]. Hence, the use of mosquito repellents from natural sources such as plants, fungi, or bacteria is preferable to the use of chemical repellents for the effective control of mosquitoes and to assure human and environmental safety where endemic mosquito resistance and environmental considerations limit their use [22]. Moreover, nanoparticles have been used as a mosquito repellent when impregnated into cotton fabrics and have shown high efficacy against mosquitoes. This gives them the potential to be used as environmentally friendly mosquito control methods [24].

2. Biological Control

Each year, promising new environmentally friendly methods are developed to gradually replace the most dangerous and hazardous methods that are used for mosquito control. Some of the encouraging outcomes include the application of biological control programs, such as genetic alteration, biological agents, predatory fish, bacteria, protozoa, nematodes, and fungi, as elaborated below.

2.1. Genetic Modification

Based on mass rearing, radiation-mediated sterility, and the release of many male insects into a defined target region to compete for mates with wild males, the sterile insect technique (SIT) is a species-specific and environmentally safe strategy for controlling insect populations. The population tends to drop when wild females mate with the released sterile males [25][26]. However, in some instances, problems associated with mosquito egg production and mass rearing have resulted in the failure of this mosquito control method [27].

2.2. Fungi

In recent years, interest in mosquito-killing fungi has revived, mainly due to continuous and increasing levels of insecticide resistance and increasing global risk of mosquito-borne diseases [28]. Indeed, when applied on mosquito resting surfaces, many fungi can infect and kill mosquitoes at the larval and/or adult stages [29]. Among them, one can cite those from the genera *Lagenidium*, *Coelomomyces*, *Entomophthora*, *Culicinomyces*, *Beauveria*, and *Metarhizium*. Notably, *Beauveria bassiana* is one of the most effective against adult *Ae. albopictus* and *Cx. pipiens* mosquitoes [30]. Unfortunately, none of these aforementioned fungi have been specifically developed as larvicidal agents against significant vector species [31][32].

2.3. Fish

Fish as predators to control mosquito aquatic stages can be introduced into all probable mosquito breeding sites [33]. Although some failures have been documented in the literature, the employment of native larvivorous fishes is recommended [34]. A small number of species are utilized, principally *Gambusia affinnis* and *Poecilia reticulata* [33]. Other water predators, especially during rainy seasons, may contribute to the decrease in mosquito populations [35] [36]. It has also been investigated if naturally occurring, non-biting *Toxorhynchites* species, which display predatory behavior throughout their larval stages, could be used as biological pesticide substitutes (the fourth instar larva is the most predaceous) [37]. Their development for use as biological agents has made significant strides, and they were remarkably effective against a variety of mosquito species, including *Ae. aegypti*, *Ae. albopictus*, and *Cx. quinquefasciatus* [37][38].

2.4. Protozoans

Protozoans are single-celled organisms that are found in almost any habitat [39]. The majority of species are free-living, but all higher animals are infected with one or more protozoa species [39]. Among them, one can cite *Chilodonella uncinata* that is a pathogenic parasite with a number of advantageous traits [40]. Indeed, in mosquito larvae, this protozoan results in low to extremely high (25–100%) mortality. When cultivated in vitro, it has a strong reproductive potential, high pathogenicity, and resistance to desiccation. Trans-ovarian transmission allows *Chilodonella uncinata* to spread in the environment through its mosquito host [18].

2.5. Bacterial Agents

There are several bacteria and metabolites from bacterial isolates with mosquitocidal properties [41]. However, the use of bacteria as sources of agents for microbial control of mosquitoes received little attention prior to the discovery of *Bacillus thuringiensis* subsp. israelensis (Bti) and *Bacillus sphaericus* (Bs) as effective mosquitocidal agents [42]. Indeed, studies have shown that Bti and Bs alone or in combination are highly efficient and safe for controlling mosquitoes, and they are thought to be safe for non-target organisms co-existing with mosquito larvae [43].

Bacillus thuringiensis produces three types of larvicidal proteins during their vegetative phase: Cry (exert intoxication via toxin activation, receptor binding, and pore formation in a suitable larval gut environment), Cyt (cytolytic toxicity) when sporulating (parasporal crystals), and Vip proteins [18]. Some of these proteins, which are toxic to a variety of insect orders and nematodes, are known to cause cancer in humans if mishandled [43]. Compared to Cry toxins, Cyt toxins are less hazardous to mosquito larvae [18]. *Bacillus thuringiensis* species, such as Bti, *B. thuringiensis* var. krustaki, *B. thuringiensis* var. jegathesan (Btjeg), *B. thuringiensis* var. kenyae, and *B. thuringiensis* var. entomocidus cause very high mortality to larval instars of all mosquitoes [44]. Other *Bacillus*-like organisms including *Clostridium bifermentans* (serovar malaysia), *B. circulans*, and *B. laterosporus* exhibit the highest toxicity against dipterans [18].

2.6. Insect Growth Regulators

Insect growth regulators (IGRs) are chemicals that mimic or compete with hormones, preventing the development of insects [45]. Among them, methoprene and pyriproxyfen, two juvenile hormone agonists, are becoming more and more popular. Other mosquito growth regulators include novaluron and diflubenzuron [45]. Insect growth regulators are a useful method for reducing mosquito populations because they are selective and have minimal environmental toxicity [18]. Insect growth regulators work well against mosquito larvae and may prevent adult mosquitoes from emerging [46][47]. A recent study has shown that mosquitoes and other pests have become resistant to routinely used IGRs such as methoprene and pyriproxyfen which highlights the need to create new control tools [48].

2.7. *Wolbachia* spp.

Wolbachia spp. are unicellular Gram-negative bacteria that are present in up to 40% of insects and other arthropods. These bacteria invade the testes or ovaries of the host and alter their reproductive potential [49]. Mosquito symbiont-associated bacteria may be harmful to their host, impairing reproduction and decreasing the vector's competence [50][51]. Additionally, *Wolbachia* spp. phenotypically cause male killing, cytoplasmic incompatibility, and pathogenicity in mosquitoes [52]. For instance, when a *Wolbachia*-infected male mates with an uninfected female, cytoplasmic incompatibility causes inviable offspring to be produced. This approach was utilized to successfully eradicate *Cx. quinquefasciatus* in Myanmar in the 1960s, and it is now used to target the *Ae. albopictus* strain with triple *Wolbachia* infections [18][53]. The development of *Wolbachia*-superinfected lines with stable infection could increase their role in lowering vector competence in *Ae. aegypti* by blocking the replication of the Dengue virus and preventing the potential emergence of resistance to the bacteria [54][55].

According to several studies, *Wolbachia* spp. prevent the spread of Zika, Dengue, Chikungunya, and yellow fever viruses as well as of *Plasmodium* parasites in *An. stephensi* and *An. gambiae* [56]. A *Wolbachia*-based vector control approach is an urgently needed to complement the biological control programs that are already fairly established, such as the use of Bti.

2.8. *Asaia* spp.

Asaia is a genus of Gram-negative, aerobic, rod-shaped bacteria from the Acetobacteraceae family that lives in tropical plants. These bacteria can colonize the midgut and male reproductive system of the mosquitoes and spread internally via the hemolymph [57][58][59]. Research has shown that *Asaia* spp. may stimulate the mosquito's immune system, preventing the growth of malaria parasites [59][60]. The genetic modification of *Asaia* spp. could enable them to colonize new hosts and propagate across wild populations [59][60].

On the other hand, the interruption of the malaria parasite transmission cycle within the vector to stop parasite development before the mosquito becomes infectious is a good way to render vectors ineffective [61]. Paratransgenesis is the easiest method for doing this, which entails creating bacterial strains that can dwell in the midguts of diverse mosquito species and spread quickly across wild mosquito populations [62]. They can then be disseminated in the mosquito population through co-feeding, sexual mating as well as paternal, maternal, and horizontal transmission [58]. A good example is the engineered transgenic *Asaia* spp. that can produce an antiplasmodial effect that makes the mosquito resistant to *Plasmodium berghei*, making it a good candidate for the control of mosquitoes and mosquito-borne diseases [63]. This approach has been used in some *Anopheles* species with promising results in terms of reduced pathogen transmission [64].

2.9. Spinosyns

Spinosyns are compounds produced from the fermentation of two species of bacteria genus *Saccharopolyspora*, family Pseudonocardiaceae. *Saccharopolyspora spinosa*, a naturally occurring soil bacterium, is fermented to produce the biopesticide spinosad that contains the insecticides A ($C_{41}H_{65}NO_{10}$) and D ($C_{42}H_{67}NO_{10}$) [65]. Spinosad is classified as a group 5 pesticide by the Insecticide Resistance Action Committee (IRAC) and belongs to a novel class of polyketide-macrolide insecticides that act as nicotinic acetylcholine receptor (nAChR) allosteric modulators [18][65][66].

In an early stage of insecticide screening, it was discovered that spinosad was active against a variety of pests in the Lepidoptera, Diptera, Thysanoptera, Coleoptera, Orthoptera, and Hymenoptera orders [18][65]. Among the mosquitoes, the spinosad pesticide has been shown to be effective in reducing larval development in *Ae. aegypti*, *Ae. albopictus*, *An. gambiae*, *An. pseudopunctipennis*, *An. albimanus*, *Cx. Pipiens*, and *Cx. quinquefasicatus* [65][67].

2.10. Bacterial-Based Feeding Deterrents and Repellents

Bacterial-based feeding deterrents and repellents are chemical substances that are derived from bacteria not to kill mosquitoes but to deter them from biting people [22]. A combination of chemicals derived from *Xenorhabdus budapestensis* (entomopathogenic-associated bacterium) is shown to deter mosquito species thought to be the most significant disease vectors influencing public health [68]. It has also been shown to be highly effective against mosquitoes, comparable to or better than DEET (N, N-diethyl-m-toluamide) or picaridin [22]. These bacteria deterrents and repellents can be coated on clothes or be made into creams and sprays [18].

3. Mechanical Control

Mechanical control methods involve the use of traps, sometimes with chemical attractants that are normally given off by mosquito hosts [69][70]. Such chemical attractants usually include carbon dioxide, ammonia, lactic acid, or octenol to attract adult female mosquitoes. Eave tubes and attractive sugar baits are some of the common examples of mechanical control methods [69].

3.1. Eave Tubes

The eave tube method comes from the mosquitoes' native behavioral ecology in sub-Saharan Africa, where they spread malaria [70]. These mosquitoes enter houses through the spaces between the roof and the walls (the eaves) [71]. As a result, closing off the eaves of houses (along with additional window screening) provides a physical barrier that protects residents from malaria [72]. Mosquitoes that enter an eave tube encounter the insecticide-treated netting inside. Eave tubes effectively convert a house into a "lure and kill" device, killing mosquitoes while also acting as a physical barrier to house access [70]. When coverage is high enough, this effect may reduce mosquito populations or change population age structures, both of which would benefit communities [70].

3.2. Attractive Sugar Baits

Attractive sugar baits are used to kill both female and male mosquitoes by taking advantage of their sugar-feeding behavior [73]. The mosquitoes are attracted to sugar baits treated with an insecticidal ingredient [73]. In laboratory and field tests, attractive sugar baits were found to be effective against Culicine mosquitoes (*Aedes* species) and sand flies [74]. When used for indoor or outdoor mosquito control, insecticide-treated sugar baits can lower mosquito populations by directly killing mosquitoes that feed on them [75].

Baits are one of the most common solutions, and their combination with other techniques, such as genetic ones, will maximize their efficiency. This is because developing mosquito-specific attractants prevents their effects on non-target species.

4. Insecticide Resistance among Mosquitoes

With the increased agricultural practices even in urban areas, the amounts of pesticides being applied to the environment have greatly increased. This has possibly favored the development of multiple resistance mechanisms among insect pests and vectors [76].

Due to selective pressure from insecticides, various mosquito species have also alarmingly developed resistance to the various mosquitocides that are currently available for their control [76][77]. This has made mosquito-transmitted infections difficult to control, leading to a great public health and economic burden, especially in tropical African and Asian countries [78][79]. The insecticide resistance of mosquitoes is mediated by various mechanisms [80]. These include mutations in the insecticide’s target site or active metabolites, enzymatic modification of insecticides to produce non-toxic metabolites, and behavioral changes or cuticle thickening. Pyrethroids and DDT have the same target site. The para voltage-gated sodium channel and knockdown resistance (kdr) mutations in this channel can result in DDT and pyrethroid cross-resistance [81].

The insensitive acetylcholinesterase (ace-1) mediates organophosphate and carbamate resistance, resulting in a single nucleotide mutation [80][81]. Metabolic detoxification is typically mediated by gene duplication or transcriptional upregulation of endogenous detoxification enzymes. These include carboxylesterase amplification, primarily through gene duplication, which results in resistance to organophosphates and carbamates. Resistance to pyrethroids and DDT is caused by increased transcription of cytochrome P450-dependent monooxygenases. Additionally, resistance to organophosphates, DDT, and pyrethroids can be caused by the upregulation of glutathione S-transferases (GSTs), which is usually caused by increased transcription rates. There have been numerous reports of insecticide-resistant mosquito species in Africa and Asia, which has resulted in an increase in mosquito-borne infections [80][82][83][84].

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