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Review Article

Fundamental Biological Mechanism and Resistance of Insect Repellent which Make Worse the Liability of Malaria in Emerging Nations

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ABSTRACT

Elimination of malaria has been successfully recorded, but still continues as a major health hazard in developing countries. As malaria control relies mainly on indoor residual spraying of insecticides, it has become a fear task due to widespread resistance in malaria vectors. However, any disease control studies taken can influence its success (vector control failures) and as a result, may have a direct effect on pathogen transmission. Currently, vector control strategies rely heavily on insecticide interventions. But unfortunately, the effectiveness of insecticide-based vector control is being overcome as mosquitoes develop resistance to insecticides. The most serious obstacles in mosquito control are insecticides resistance. This review has shown that insecticides are involved to eliminate vector-borne diseases. Therefore, effective management should be designed to monitor insecticide resistance at regular intervals.

Keywords: Insecticides; Malaria; Resistance mechanism; Vector borne diseases; Vector control

INTRODUCTION

Malaria is a major health concern around the world has a profound socio-economic where it's endemic [1]. In 2015, an estimated 429,000 deaths occurred through malaria to children below the age of 5 in Africa. Furthermore, an estimated 92% of malaria deaths occurred in Africa [2]. When taking the history of the dry zone of Sri Lanka, malaria was a leading cause of morbidity and mortality [3]. Yet, since October 2012 there has been no case of indigenous malaria reported in Sri Lanka. As a result, in 2016 Sri Lanka has been certified by the WHO as a country eliminated from malaria which was a life-threatening disease [2]. Furthermore, it is of vital importance for research to continue and to understand the impact of its problems. Also, find ways to manage the growth in insecticides resistance. This review showed the biological mechanism of insecticides that control malaria. For Indoor Residual Spraying (IRS), several strategies have proposed which might prevent or slow down resistance. Vector control remains one of the central components for malaria control through larval source reduction and adult vector control [4].

Insecticides

Insecticide resistance in pest populations affects both the economy and public health at a worldwide scale: it decreases crop yields (and thus profitability), induces the need to increase the quantity of insecticide and to develop new insecticides (thereby having a strong impact on costs and the environment), and finally it is responsible for an incidence of human or animal diseases [5,6]. Resistance is defined as a heritable decrease of the susceptibility to an insecticide [7].

Three categories of resistance can be distinguished: behavioral (avoidance of contact with insecticide), physiological (e.g., increased cuticle thickness), and biochemical (enhanced insecticide detoxification and sequestration and/or decreased insecticide target sensitivity). Few examples of behaviors such as *Anopheles gambiae* on Bioko Island and Senegal [8,9] or *Anopheles funestus* in Benin and Tanzania [10] and physiological resistances have been reported; whether they are heritable remains debated, and it is difficult to assess the level of protection they provide [11].

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Biochemical resistances typically result in a relatively high level of protection and are genetically determined. Resistant individuals carry one or several genetic mutations that prevent insecticide disruption of the target functioning. As a result, the frequency of resistance gene(s)/allele(s) increases in the population over time. Insecticide resistance is confirmed by toxicological tests (bioassays) establishing resistance ratio (or RR corresponding to the number by which an insecticide dose must be multiplied to obtain the same mortality in resistant than in susceptible insects). It can be investigated at many levels, from the molecular characterization of genes/alleles conferring resistance and their biochemical products to the effect of these genes on the fitness (i.e., mean reproductive success) of the individuals carrying resistance alleles, to the dynamics and evolution of these resistance alleles in natural vector populations and their effect on disease control [12].

The first case of resistance has reported in 1908, in a population of San Jose scale (*Aspidiotusperniciosus*) resistant to lime sulfur [13]. A century later (2007), 553 arthropod species have reported as resistant to at least one insecticide, among many disease vectors. More than 100 mosquito species are resistant to at least one insecticide (including 56 *Anopheles* species, 39 Culicine species), *Culexpipienspipiens* and *Anopheles albimanus* are resistant to more than 30 different compounds [6].

Synthetic insecticides

Four major classes of organic (synthetic) insecticides are used to control insects: the organ chlorines (OCs), the organophosphates (OPs), the carbamates (CXs), and the pyrethroids (PYRs), with, 4429, 1375, 30, and 414 metric tons respectively, of active ingredient used annually for global vector control from 2000 to 2009 [14]. The use of synthetic insecticides was started back in 1943 for control of malaria. The first synthetic insecticide was DichloroDiphenylTrichloroethane (DDT) and later cyclodiene (CD) dieldrin was started to use. [15-19]. From the late 1970s, the PYRs class of vector control replaced OCs, and these became widely used in malaria vector control. They are today by far the most-used insecticides, with 81% of the World spray coverage [14]. PYR-based Indoor Residual Spraying (IRS) and Insecticide-Treated Nets and curtains (ITNs) are currently advocated as standard malaria vector control strategies. Finally, two other classes of synthetic insecticides are used at a large scale worldwide: the OPs and the CXs, which were first used in the 1940s and the 1950s, respectively [7,15].

They are usually used as larvicides (although some are now considered for ITN impregnation and IRS as an alternative to PYR, and are particularly well suited for species with delimited breeding sites [20]. OCs and PYRs are highly popular due to their very low toxicity to human and long half-life in the environment, which makes it more cost effective in vector control. On the other hand, OPs and CXs have a short half-life; and two to three rounds of IRS are needed per year. This significantly reduces the cost-effectiveness of the use of these two classes of insecticides. However, when compared to OCs and PYRs these two groups evidently have less potential of developing resistance [21]. Furthermore, the latter two groups have less environmental impacts due to their lower half-life in the environment than OCs and PYRs. Some new groups of insecticides such as neonicotinoids, phthalic acid diamides, or anthranilic acid diamides were introduced in the 2006-2008 period. However, these groups did not become much popular in disease vector control despite their popularity in agricultural pest control [6,22].

During the same period, another group of synthetic insecticides was introduced. These interfere with insect physiological processes by mimicking certain compounds produced in the endocrine system. Synthetic Insect Growth Regulators (IGR) is one of the best examples of this. Furthermore, synthetic products called juvenoids [23] that mimic the juvenile hormone (JH) and chitine inhibitors [24] are also some examples for this.

Mechanisms of resistance

The targets of most insecticides are critical proteins of the insect nervous system. Insecticides bind to specific sites on their targets and disrupt their function. Any mechanism that decreases the insecticide effect will lead to resistance. This encompasses reduced penetration of the insecticide, increased excretion or sequestration of the insecticide, increased metabolism of the insecticide, and finally target modification that limits the binding of the insecticide [8,11]. The first three mechanisms are poorly documented and do not seem to play a prominent role in resistance [25].

Metabolic resistance

Metabolic resistance includes the various mechanisms that lead to the degradation of the insecticide in less or nontoxic products, thus decreasing the number of toxic molecules that reach the target. The detoxification through enzymatic reactions is one of the major ways of metabolic resistance. There are several groups of enzymes involved in this type of resistance mechanisms. For instance, Glutathione S-Transferases (GSTs), carboxylesterases (COEs) and cytochrome P450 monooxygenases (P450s) are three of the major groups [26]. Among these GSTs catalyze the reaction between sulfhydryl group and electrophilic sites of xenobiotics and form conjugates that are more readily excreted and typically less toxic than the parent insecticide and this group associated with resistance to OCs, particularly DDT, and OPs COEs on the other hand, act by binding to an ester group on the xenobiotic molecule and then break the ester bound by a process of acylation, de-acylation [18,27]. The majority of insecticides, including almost all CXs and OPs, most PYRs, and some IGRs bear ester groups; hence resistance may develop due to the action of COEs [Pasteur N., 1984]. The other group, P450s involved in detoxification through monooxygenase activity and is responsible for the resistance to several groups of insecticides, particularly DDT, PYRs, and CXs [19,28].

Target-site modification

Resistance by target-site modification is due to point mutations in the insecticide target gene that results in reduced binding of insecticides. For an instance resistance to CDs may develop due to a decreased sensitivity to insecticide of the GABA receptor A, through a point mutation causing an amino acid change in the

receptor-coding gene. The extensive use of CDs before their banning in the 1980s resulted in resistance in several insect species [29,30].

Voltage-gated sodium channels (vgscs)

VGSCs are glycoproteins with a pore for ion transport and can adopt three different states: resting, open, or inactivated; the Na + ions pass only when the channels are open [31]. VGSC are the targets of DDT and PYRs. When these insecticides bind to the VGSC, they slow their closing speed, prolonging the depolarization [32]. One major mechanism, named knockdown resistance (kdr), is responsible for PYR and DDT resistance, by reducing the sensitivity of the receptors (binding capacity) to these insecticides and modifying the action potential of the channel [23,32,33].

Acetylcholinesterase (Ache)

AChE is the target of OPs and CXs insecticides, which are competitive inhibitors of AChE when they bind to AChE; their very slow release prevents hydrolysis of the natural substrate. Consequently, AChE remains active in the synaptic cleft and the nervous influx is continued, leading to insect death by tetany. In most insects, there are two genes, ace-1 and ace-2, coding for AChE1 and AChE2, respectively. In these species, AChE1 is the main synaptic enzyme while the physiological role of AChE2 is still uncertain. *Diptera* of the *Cyclorrapha* group or "true" flies (such as *D. melanogaster* and *M. domestica*) possess a single AChE, which is encoded by the ace-2 gene and is the synaptic enzyme in that case. In mosquitoes where AChE1 is the synaptic enzyme, the most common resistance mutation (G119S) in the ace-1 gene is located just near the active site [34-36].

Other resistance mechanisms

Growth regulators: Juvenoids mimic JH and disrupt insect development. Few resistance cases have been described in various species. High resistance to methoprene has been described in the mosquito *Ochlerotatus nigromaculis* in California, potentially through target-site mutation [37]. While, 7.7-fold resistance have been reported to the same insecticide in *C. pipiens* from New York [38].

Toxin receptors: *Bacillus thuringiensis* (Bt) toxins have a complex mode of action not clearly understood. Bt resistance is increasing in the field in several pests [39]. Presently, the only report of field resistance in the mosquito is a 33-fold resistance to Bti (*Bacillus thuringiensis var. israelensis*) the only Bt variety active on mosquitoes) detected in a natural population of *C. p. pipiens* from New York. However, the mechanism of this resistance was not investigated [38]. Genomic studies suggested several candidates for Bti resistance in *Ae. Aegypti*, but they are not yet validated [28] finally; it appears that depending on the environmental conditions, some of the four Bti toxins may be inactivated, which could favor the emergence of full Bti resistance through intermediate bouts of selection to each toxin independently [40]. For *Bacillus sphaericus* (Bs) toxins, resistance has been described essentially in mosquitoes of the *C. p. pipiens* complex, due to a mutation in the toxin receptor. It developed very rapidly within the first year of treatment in India [41] and in Tunisia [42]. Similarly, control using Bs toxins started in the early 1990s in Southern France and first failure was reported in 1994 in Port-Louis (near Marseille). This resistance was due to a recessive sex-linked gene, named sp-1. In 1996, Bs resistance was reported close to the Spain border it was due to a second gene, sp-2, which was recessive and sex-linked [43]. Now Bs resistance has been observed worldwide in the *C. p. pipiens* complex [41]. Two of the alleles identified (sp-2R and an allele selected in a laboratory strain from California [44] change the toxin receptor binding properties and were found to be due to "stop" mutations or mobile element insertion in the toxin receptor [45,46].

CONCLUSION

Vector control remains a powerful and accessible tool to control these diseases and upgrade the socioeconomic burden they cause in developing countries. However, any disease control studies taken can influence its success (vector control failures) and as a result, may have a direct effect on pathogen transmission. This includes first establishing a continuous survey of resistance at a local scale by implicating the local population, a difficult but essential task to set goals and evaluate success. Several survey sites in different conditions are required for sentinel purposes, together with some baseline information, to rapidly detect resistance, identify the mechanisms, and change the policies adequately. These local surveys should then be integrated at a more global scale for vector control coordination, allowing informed decisions for using alternative tools to insecticides and preserving the remaining insecticides by carefully planning their use to minimize resistance selection.

Variation in insecticide resistance mainly depends upon the type of insecticide and frequency of use. Although various mechanisms of insecticide resistance in insects such as metabolic resistance (i.e. esterases, monooxygenase or glutathione-s-transferase), resistance due to reduced penetration or behavioral resistance are reported in several vectors, generally it is governed by either involvement of metabolic mechanisms or alterations at target sites. Revealing the mechanism of resistance is equally important to that of monitoring resistance in mosquito vectors. An *Anopheles* species are highly resistant to DDT. Insecticide resistance is a serious emerging problem in Developing countries.

Currently, the national program has no alternative insecticide for effective vector control or for insecticide resistance management. There are some insecticides available for vector control, an approach focused on the rotational use of insecticides or a mosaic strategy can be adapted to delay development of resistance in malaria vectors. Also, highlighting needs to be given to other eco-friendly methods of vector control, such as bio control with larvivorous fish and biolarvicides especially *Bacillus thuringiensis var. israelensis* included in the integrated vector management program. Effective resistance management mainly depends upon early detection of the status of resistance, therefore monitoring of insecticide resistance at regular intervals is necessary so that an effective management strategy can be designed.

CONSENT FOR PUBLICATION

We certify this manuscript has not been published elsewhere and is not submitted to another Journal.

COMPETING INTERESTS

The author(s) declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

LS and AD conceived the study design, interpreted and manuscript preparation. SMT and MS are drafting of the article details with an edit the manuscripts. All authors read and approved the final manuscript.

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