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Mosquito Resistance to Insecticides in Ethiopia: A Review Article

Gebrehiwet Tesfahuneygn[1*] Gebremichael Gebreegziabher[1]

[1]Tigray health research institute, Mekelle

***Corresponding Author:** Gebrehiwet Tesfahuneygn, Tigray health research institute, Mekelle, Ethiopia.Email:gtlab2006@gmail.com*

ABSTRACT

***Objectives:** The aim of the study was to know the status of insecticide resistance to mosquito in Ethiopia. As well as what questions were answered and for next what questions needed to be answered.*

***Results:** Extreme resistance to DDT and pyrethroids was insidious across Ethiopia, related with historic use of DDT for indoor residual spray and concomitant increases in insecticide-treated net coverage over the last 17 years. Longitudinal resistance trends to malathion, bendiocarb, propoxur and pirimiphos-methyl corresponded to shifts in the national insecticide policy. DDT resistance was widely distributed in Ethiopia and DDT was replaced by deltamethrin. Moreover, in 2012 Ethiopia switched from deltamethrin to bendiocarb for indoor residual spray in response to the observed resistance. All the study that conducted in Ethiopia were only focused on mosquitoes that are vectors for malaria.*

Keywords: *Mosquito, Insecticide resistance, Ethiopia*

INTRODUCTION

Insect vectors accounts for almost 20 per cent of all infectious diseases affecting people in developing countries [1]. Significant vector borne diseases, such as malaria, typhus fever, yellow fever, and insect borne enteric infections, have been controlled effectively in certain parts of the world and nearly eradicated in others through the use of insecticides[2].There are four main classes of neurotoxic insecticides that are recommended or prequalified by WHO for indoor residual spray (IRS) namely: carbamates, organochlorines, organophosphates and pyrethroids, But only pyrethroids are recommended for insecticide-treated nets (ITNs) due to their relatively low toxicity to humans, a rapid knockdown effect on mosquitoes, and low cost [3]. From the time when pyrethroids are introduced for ITN impregnation in the 1980s, no new adulticide has been approved for ITN treatment [4].

The mechanisms of insecticide resistance vary widely, as target sites and mechanisms of degradation can differ among insecticides. These classes of insecticides mainly target receptors in the mosquito's nervous system or inhibit enzymes involved in transmitting nerve impulses, causing paralysis and insect death. Some target sites are shared by different classes of insecticides. DDT and pyrethroid insecticides act through the receptor for the voltage-dependent sodium channel (CNaVdp), organophosphates and carbamates target acetylcholin esterase (AChE), and cyclodiene insecticides target the gene coding for the gamma-aminobutyric acid (GABA) receptor[5]. Resistant strains have mutations in target sites or genes that code for enzymes that impact the effectiveness of a specific insecticide.

Even though insecticides are quite effective when used according to technical indications, some of the factors that affect insecticides effectiveness are the use of poor quality insecticides of or adulterated processes of resistance in insects, failures in the processes of preparation and application, among others [6].The development of resistance to insecticides by many insect vectors which transmit diferent diseases, threatens the continuation and extension of worldwide progress in the control of vector borne diseases. For this reason, insect resistance is internationally recognized by leading health authorities as the most important problem facing organized vector borne disease control programs [7]. Different insect vectors have developed resistance due to mismanagement of the insecticides used [8]. Resistance can be

understood as the inability of an insecticide used according to the technical indications to achieve an adequate control of a pest or group of pests, due to genetic modifications in the target species, which make them less sensitive to the applied product [9].

About 325 insecticides already have technical reports of resistance by one or more species [10]. Different levels of resistance have been found in the different classes of insecticides. DDT, organochlorines, carbamates, organophosphates, pyrethroids and pyrethrins are the chemical groups that present a higher level of resistance, mainly due to their diversity of chemical compounds, and for the long time of use in the market; however, in other insecticides considered as new generation, resistance reports also have been found [11].

The mechanisms of resistance can be divided into two main groups: physiological and behavioral. Physiologically, the resistance can be presented by changes in the site of action of the insecticide, due to specific mutations in the receptors, which limits the ability of the toxic to bind to the receptor molecule, or affects its function after the union. The second mechanism of resistance is biotransformation, which involves the metabolic destruction of the insecticide within the organism, by means of biochemical processes such as hydrolysis, oxidation or conjugation [12], wherever some enzymes play a preponderant role such as esterases, glutathione-S-transferases and cytochrome P450 monoxygenases [13]. Resistance can also occur because of a reduction in the rate of cuticular penetration, which prevents the insecticide from reaching its lethal concentration, and on the contrary allows the body to metabolize and eliminate the drug with minimal or absent toxic effects. Finally, physiological resistance can occur due to the binding of the insecticide with non-objective macromolecules, so it does not exert any toxic action [13]. On the other hand, behavioral resistance should be understood as the heritable capacity of an insect to avoid contact with an insecticide, which results in a measurable decrease in susceptibility to a toxic [14].The pyrethroid chemical family is described as having low toxicity on humans. Insecticidal molecules belonging to these four families target different ion channels or enzymes to interrupt the proper functioning of the insect nervous system [15].Mutations in the amino-acid sequence of binding site of the insecticide target as well as metabolic changes, lead to frequent resistance in mosquito populations [16]. After decades of insecticide pressure, mosquito populations have become resistant to multiple chemical insecticide families, compromising the effectiveness of chemical-based control [17, 18].

Unluckily, in the last decade pyrethroid resistance has become widespread in Anopheles genera in Sub-Saharan Africa [18]. This was mainly driven by the high selective pressure stemming from the huge use of pyrethroids in agriculture [19, 20] and the scaling-up of pyrethroid ITNs and IRS for malaria control [21]. Although the epidemiological impact of resistance mechanisms on vector control remains controversial, numerous reports of pyrethroid resistance have discovered reduced vector mortality and a consequent drastic loss of personal protection conferred by pyrethroid-treated nets to humans [22]. Sixty one countries reported mosquito resistance to at least one insecticide used in nets and IRS [23]. This situation represents a serious threat to the efficacy of malaria control tools. The WHO recommends the use of insecticide combinations with different modes of action for LLIN impregnation in order to manage pyrethroid resistance in malaria vectors; the underlying hypothesis is that insects that can survive contact with one component of the mixture would be killed by the second insecticide [24,25]

Chlorfenapyr has been shown to have the potential to provide improved control of pyrethroid-resistant An. gambiae both in laboratory and in controlled conditions against natural free-flying resistant malaria vectors [26]. A mixture of chlorfenapyr and alpha-cypermethrin on bed nets has been shown to provide excito-repellency and strong insecticidal activity against pyrethroid resistant mosquitoes [27, 28]. Recently, BASF® developed a long-lasting insecticidal mixture net, called Interceptor G2, that is made of polyester fibers and treated with a mixture of alpha cypermethrin/chlorfenapyr. The World Health Organization Pesticide Evaluation Scheme (WHOPES) reviews and makes recommendations on new pesticide technologies for public health programs, such as LLINs[29].

Main Text

Results

There are local evidences showing the widespread of insecticide resistance to various

chemicals used for IRS. Intense resistance to DDT and pyrethroids was persistent across Ethiopia, consistent with historic use of DDT for IRS and concomitant increases in insecticide-treated net coverage over the last 17 years. Longitudinal resistance trends to malathion, bendiocarb, propoxur and pirimiphos-methyl corresponded to shifts in the national insecticide policy. By 2016, resistance to propoxur and pirimiphos-methyl insecticides had emerged, with the potential to jeopardize future long term effectiveness of vector control activities in these areas. Between 2015 and 2016, the West African (L1014F) *kdr*allele was detected in 74.1% (n = 686/926) of specimens, with frequencies ranging from 31 to 100% and 33 to 100%in survivors from DDT and deltamethrin bioassays, respectively. Restoration of mosquito susceptibility, following pre-exposure to PBO, along with a lack of association between *kdr*allele frequency and *An. Arabiensis* mortality rate, both indicate metabolic and target-site mutation mechanisms are contributing to insecticide resistance [30]. DDT resistance was widely distributed in the country and DDT was replaced by deltamethrin. Moreover, in 2012 Ethiopia switched from deltamethrin to bendiocarb for IRS in response to the observed resistance. Populations of An. arabiensis were resistant to DDT and deltamethrin but were susceptible to fenitrothion inall the study sites. Reduced susceptibility to malathion, pirimiphos-methyl, propoxur and bendiocarb was observed in some of the study sites. Knockdown resistance (kdr L1014F) was detected in all mosquito populations with allele frequency ranging from 42 to 91%. Elevated levels of glutathione-S-transferases (GSTs) were detected in some of the mosquito populations [31].

In Ethiopia, target site resistance mechanism in populations of An. arabiensis was first reported from areas around the Gilgel Gibe hydro-electric dam, southwestern Ethiopia. The kdr allele frequency of the L1014F mutation in the Gilgel Gibe region was the highest ever reported in An. arabiensis [32]. Subsequent studies have also documented the same mutation in this species in other parts of the country [33–35].

DISCUSSION

Anopheles gambiae s.l. was sensitive to DDT only in 2 of 16 localities where susceptibility studies were carried out in northern Ethiopia; it was resistant in 11 sites and potentially resistant in three. To malathion, the test population was sensitive in four of the six study sites in southern Ethiopia and potentially resistant in the other two sites. In northern Ethiopia, the population was resistant in five localities and sensitive in three. Of the six localities in northern Ethiopia where permethrin was tested, populations were sensitive in three, resistant in one and potentially resistant in two. In southern Ethiopia, the populations were resistant in five of the six sites. Against deltamethrin, the population was sensitive in five of 13 localities, three in northern and two in southern Ethiopia. It was resistant only in two localities, one in northern and one in southern Ethiopia, and potentially resistant in five localities. In eastern Ethiopia at Sabure, the population was sensitive to all insecticides but DDT to which it was potentially resistant [36].

The mechanisms responsible for insecticide resistance are complex and include behavioral and/or physiological changes of mosquitoes leading to insecticide avoidance, altered penetration, sequestration, target site alteration or bio-degradation. In mosquitoes, resistance is mainly associated with target site modification and metabolic resistance. Target site resistance involves mutations leading to well defined target site alteration and resistance to chemical insecticides [37].Metabolic resistance, on the other hand, involves more subtle alterations in the expression of a complex array of enzymes and detoxification pathways [38,39], the mechanisms of which are far less well understood. Metabolic resistance occurs through increased bio-degradation of the insecticide, usually through overproduction of detoxification enzymes such as P450s, glutathione S-transferases (GSTs) and carboxy/ cholinesterases (CCE) [39]. Of these, P450sare the primary enzyme family associated with resistance to most insecticides including pyrethroids, the most widely used class of insecticide for vector control. Elevated levels of P450s activity are frequently observed in pyrethroid-resistant malaria vectors in Africa [37,40-44]. Esterase hydrolysis of pyrethroids leading to detoxification is also believed to act as a cause of metabolic resistance in some instances [45], while GSTs are regularly found over expressed in pyrethroid-resistant strains [46]. However, the contribution these enzymes make towards pyrethroid resistance and their biochemical relationships with P450-mediated resistance is still unclear. Several P450s in An. gambiae associated with pyrethroid resistance includes CYP6Z1, CYP6Z2, CYP6M2, CYP6P3

and CYP325A3 [44,47,48]. Of these, CYP6P3 and CYP6M2 have appeared most widely over-transcribed in resistant field populations [43,44].Importantly, they have been shown to metabolize permethrin and deltamethrin [49,50], thus operationally are considered key diagnostic markers of resistance. Most recently, high levels of CYP6M2 gene expression have been found in a highly DDT-resistant population of An. gambiae from Ghana, using a novel whole genome microarray [51]. Likewise, CYP6Z1 has been found over expressed in both pyrethroid and DDT resistant strains, and shown to metabolize DDT [52], placing it in the frontline of metabolic resistance markers for DDT.

Resistance mechanisms in An. funestus, the second major vector of malaria in Sub-Saharan Africa, the use of quantitative trait loci (QTL) has identified CYP6P9, CYP6P4, CYP6Z1, CYP6Z3 and CYP6M7 as being strongly associated with pyrethroid resistance [53,54]. CYP6Z1 and CYP6Z3 have already been linked with insecticide resistance in An. gambiae, while CYP6P9 and CYP6M7are orthologues of An. gambiae resistance markers, CYP6P3and CYP6M2, respectively. To date, increased levels of CYP6P9 have been most frequently observed in pyrethroid-resistant laboratory and field populations from Mozambique [40, 41, 53, 55, 56], Uganda [57] and Benin [58].

CONCLUSIONS

Pyrethroid resistance is now wide spread in Sub-Saharan Africa. Novel insecticides to manage pyrethroid resistance are critical to maintain the efficacy of malaria vector control. The pyrrole insecticide chlorfenapyr has been identified as a novel insecticide of interest to public health. In Ethiopia, we have found studies only related to insecticide resistance to malaria vector mosquito.

Limitation

The limitation of this study is we reviewed only those which were accessed in online as open access.

DECLARATIONS

Ethics Approval and Consent to Participate

Not applicable

Consent for Publication

Not applicable

Availability of Data and Material

Data is available in PDF and MS word

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Competing Interests

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTION

GT and GG wrote and edited the manuscript. All authors read and approved the final manuscript.

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