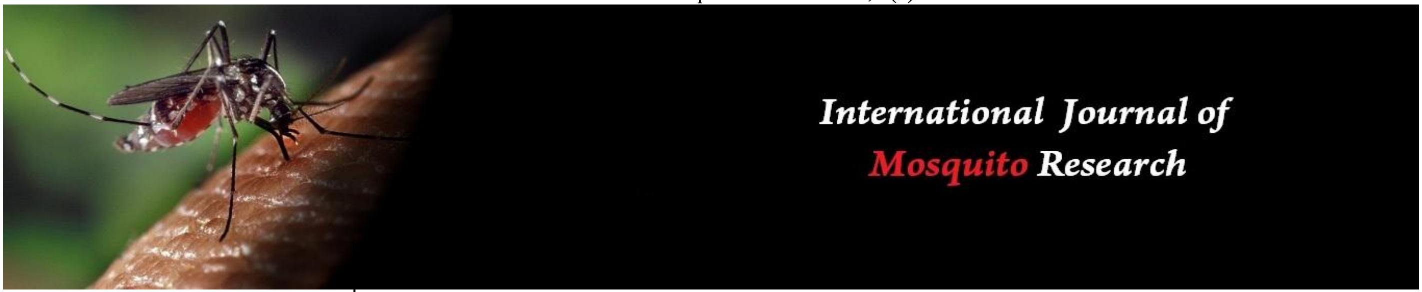

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Insecticide resistance in mosquitoes: An overview and strategies to mitigate insecticide resistance development

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Abstract
The resistance of pathogen vectors that cause human or animal diseases to insecticides affects both the economy and public and veterinary health. The aim was to present the main mechanisms of resistance to insecticides as well as the current situation in terms of resistance to chemical insecticides in the main mosquito vector in Tunisia. Management strategies were done so that pesticides can continue to be used as crop management tools in the future. In such cases, the strategy chosen to resistance management must be based on thorough knowledge of the resistance implications of the used insecticides and the biology of resistant vectors. Implementation of insecticide resistance management strategies or preservation of insecticide susceptibility is now inevitable due to the increase in the number of species developing insecticide resistance mechanisms and the decrease in the number of insecticides.

Keywords: Insecticide resistance, mosquitoes, vectors, public health, managing resistance

1. Introduction

In Tunisia, an intensive control program was carried out in the framework of the National Program for the Eradication of Malaria between 1968 and 1974 against *Anopheles* mosquitoes, malaria vectors, mainly through the use of DDT, pathology has disappeared from the country since 1979 [1].

In recent decades, the expansion of urban and industrial development contributed significantly to the creation of favorable breeding sites with a great extension of *Culex pipiens* mosquitoes [2] in Tunisia. Indeed, *Culex pipiens* mosquito is known by their remarkable plasticity conferring their ability to colonize all the types of shelters, relatively clean or polluted. Their density reaches very high values [2, 3].

On the other hand, *Culex pipiens* may be involved in the transmission of West Nile virus (WNV) in the two outbreaks of West Nile fever, occurred in the country [4] in 1997 and 2003. Indeed, *Culex pipiens* was the most abundant species in areas where clinical cases were reported. It should be noted that the vectorial role of *Culex pipiens* in WNV transmission was reported in Egypt [5], Palestine [6], India and Pakistan [7, 8], Europe and Russia [9, 10, 11], and the United States [12, 13].

In addition to its potential for the transmission of pathogens to humans, *Culex pipiens* is a source of nuisance to the population, particularly in urban and peri-urban areas. As a result, operators in the field of mosquito control have not stopped fighting these insects using different insecticides. In this way, *Culex pipiens* mosquitoes has acquired resistance to many used insecticides [14-18].

Preliminary work on the resistance to insecticides of mosquitoes in Tunisia was carried out in 1989 by Kooli and Rhaïem. These authors showed that resistance to chlorpyrifos, an organophosphate insecticide, is moderate, rarely exceeding 15 times, in *Culex pipiens* samples taken in the Tunis during the period 1984-1988. Later, very high levels of resistance to chlorpyrifos and pyrethroid permethrin, were recorded in *Culex pipiens* samples collected between 1990 and 1996 in a few localities in the country [19-21].

Despite all the problems related to the use of insecticides, this practice remains the most used way in the fight against *Culex pipiens* in Tunisia. This is due to the relatively easy use of these products, the limited technical and operational capacity of the operators to carry out the recommended remediation work, and the difficulty of implementing alternative methods of control. This causes the amplification and the spatial extension of the resistance. However, the reduction in the number of active substances available, the emergence of resistance to the main families of insecticides and the need to respect the environment as a whole justify the implementation of an in-depth reflection on the use of these substances and the management of resistance phenomena in mosquito's vectors. This monitoring based on the realization of bioassays and the search for mechanisms of resistance must make it possible to adapt the control strategy according to the observed results.

It is in this context that this document is inscribed. The aim was to present the main mechanisms of resistance to insecticides as well as the current situation in terms of resistance to insecticides in the main mosquito vector in Tunisia. On this basis, proposals were made for the rational use of insecticides and a sustainable strategy for the management of resistance phenomenon.

2-Mechanisms of resistance to chemical insecticides

The resistance of pathogen vectors that cause human or animal diseases to insecticides affects both the economy and public and veterinary health globally. It makes the available products and vector control strategies inefficient, thus leading to an increased prevalence of the pathogens and diseases they transmit [22-24]. Agriculture, as part of the control of crop pests or food stocks, remains by far the sector that uses the most insecticides. Approximately 3 million tons of pesticides are applied worldwide each year for an annual amount of about US $ 40 billion. Resistance to pests leads to an additional cost of $ 1.5 billion per year for agriculture in the United States [25]. On the other hand, very little economic data is available concerning the cost of resistance of the main vectors of human or veterinary pathogens interest. The first case of resistance dates from 1908 in the pest *Aspidiotus perniciosus*, a cochineal, resistant to lime sulfur [26]. A hundred years later, 553 species of arthropods are reported to be resistant to at least one insecticide, including many vectors of pathogens such as mosquitoes, lice, bugs, triatomes, fleas, and ticks.

The resistance of a target species can be defined as an inheritance reduction of susceptibility to an insecticide [23]. At the fundamental level, this is an adaptation to the new environment selected by the pressure exerted by one or more insecticides, according to a natural selection process. Resistant individuals carry one or more gene mutations (known as resistance alleles) encoding proteins that interact with the insecticide. Thus, the mutated proteins prevent the insecticide from reaching its target, for example by degrading it, or by modifying this target, enabling the insects carrying these mutations to survive doses of insecticide that are normally lethal. Insecticides do not cause these mutations to occur directly, but select the individuals who carry them, as they are then able to survive and reproduce in the presence of these insecticides. As a result, the frequency of the resistance allele (s) increases in populations exposed to the insecticide over time. Some species may be resistant to a very wide range of chemical compounds, so called "cross-over" resistance when a single mechanism confers resistance to different insecticides and "multiple" resistance when several different mechanisms confer resistance to different insecticides [24].

When resistance is suspected, for example due to a reduction in the effectiveness of insecticide treatments in the field against a target species, the level of resistance of the population is first evaluated by laboratory toxicological tests (bio-tests) Which make it possible to establish resistance levels or ratios (RR) by comparison with a reference sensitive strain of the same species. It is also possible to search for known biochemical genes or markers to intervene in resistance in order to determine their frequency and to follow their evolution in the target populations.

Although the general mechanisms leading to insecticide resistance in vectors are increasingly well known, not all are characterized at the molecular level for each species and for each molecule, which may compromise the early detection of resistance to ground. The detection of known target mutations targeted by the currently available insecticides is now possible through the use of simple molecular tests. However, these molecular tests are not yet available for all species of medical, veterinary and economic interest. Knowledge is more fragmented in the case of metabolic resistance. Research is still needed to identify the genes involved in this type of resistance and better assess their real impact on operational level resistance in the field; and develop diagnostic tests to detect and characterize the resistance of before it is more manageable in an operational manner.

In general, the identification of resistance mechanisms in vectors will help to improve the use of insecticides in vector control. A better understanding of the mechanisms of insecticide resistance to better detect and manage it appears to be a major issue, but requires a major research effort. This effort must be carried out in the long term in close coordination with the operators involved in the field of vector control.

3-Mosquitoes resistance status in Tunisia

An inventory of the resistance to insecticides of the different arthropod vectors subjected to vector control in Tunisia was drawn up. A survey was carried out in the operational departments (Department of Hygiene and Environmental Protection) and, on the other hand, a literature search focused on "resistance to insecticides" for the different species of vectors of interest in Tunisia [19-21, 27]. These elements show a fragmentary knowledge of resistance at both the geographical level and the considered vectors.

The vast majority of data collected relates to culicidae. *Culex pipiens* is logically the most well-resistant species in which it is regularly controlled because of its role as a potential vector for West Nile virus. Resistance to organophosphates and pyrethroids was particularly observed [19-21, 27, 28].

4-Anticipate and prevent vector control failures through the use of insecticides

Observation of insecticide resistance in a vector population is not necessarily associated with treatment failures. Indeed, the resistance must be widely distributed among the target population in order to have a visible operational impact. In addition, some insecticides have, in addition to their lethal action, a repellent action. For permethrin, for example, the major effect of which is repulsion, resistance can have only a limited effect on the overall effectiveness of the intervention. However, it is essential to detect as soon as possible the appearance of resistance, in order to allow operators to adapt their control strategy, both in terms of choice of active substance and methods of application which may vary depending on of the product and its formulation.

The implementation of methods for monitoring the sensitivity of target species to insecticides varies widely among public operators. Although some of them regularly perform tests on both larvae and adults, and attempt to characterize the mechanisms involved in resistance in partnership with research laboratories, most of them only perform larval bioassays with variable frequency. Others rely solely on evaluating the efficacy of treatments to assess sensitivity.

In view of the reduction in the number of active substances available in vector control, it is becoming increasingly imperative to preserve the effectiveness of existing molecules, which are difficult to substitute in the event of resistance in the targeted vectors. Thus, WHO promotes the development of insecticide resistance management strategies even before resistance is reported. Such anticipation must be an integral part of vector control programs.

5-Management Strategies for Insecticide Resistance

Implementation of insecticide resistance management strategies or preservation of insecticide susceptibility is now inevitable due to the increase in the number of species developing insecticide resistance mechanisms and the decrease in the number of insecticides.

Management of resistance to insecticides requires the implementation of an integrated control strategy based on the various control methods available and making it possible to limit as far as possible the use of biocidal active substances. Resistance management must be an integral part of any control strategy. In the current context of scarcity of insecticides that can be used in public and veterinary health, resistance management should be seen primarily as a prevention tool and should not only be considered as the possibility of restoring the sensitivity of vectors once the Resistance is installed.

5-1-Rotation of insecticides

This type of strategy is based on the use of several insecticides with different modes of action, alternating over time. Such an approach is based on the fact that the emergence of a resistance induces a cost at the level of the targeted vectors, so that the installation of different resistance mechanisms is unlikely if we do not allow time for a mechanism in to settle because of its genetic cost.

The rotation must be performed at a sufficiently short frequency. In the case of treatments of human disease vectors, an annual rotation is generally sufficient.

The OCP (Onchocerciasis Control Program) program in West Africa is the most emblematic example of a successful strategy for vector resistance management in public health. After the first cases of resistance to temephos (OP) in the blackflies in 1980, a rotation of 7 insecticides belonging to 4 families was set up for anti-larval treatments. This strategy resulted in a reduction in resistance to organophosphates and the maintenance of susceptibility to blackflies to these 4 insecticide families for the next 20 years of the program, thus ensuring the long-term effectiveness of vector control [29].

In South Africa and Equatorial Guinea, operational failures of pyrethroids were reported in intra-household spraying. The populations of anophelines highly resistant to pyrethroids could be controlled by the use of carbamates or DDT [30, 31].

5-2-Mixtures and combinations of insecticides

The use of mixtures of insecticides with different modes of action results from the low likelihood of the concomitant emergence of several mechanisms of resistance. This is the same principle used for multitherapy against certain bacteria or HIV. Consequently, simultaneous use, either in the same slurry or by successive application, is such as to preserve the sensitivity of the insect vectors to the insecticides.

The use of this type of strategy theoretically requires its use prior to any installation of resistance to any of the used substances.

Insecticidal-insecticidal, insecticidal-synergistic or insecticidal - repellent combinations can produce a synergistic effect capable of increasing the duration of effectiveness of the active substances, reducing effective doses and also having an insecticidal action on resistant insects when used alone [20].

It should be noted that industrialists have to re-certify for any mixture even if the substances which constitute it are already registered because of a synergizing risk, which implies additional development costs.

These strategies can be implemented by the use of several insecticides to impregnate the various parts of a mosquito net or a dwelling. Small-scale trials of mosquito-treated mosquito nets and intra-home impregnationhave shown good results against pyrethroid-resistant mosquitoes. However, their interest in slowing down the development of resistance at the operational scale has not yet been demonstrated [32].

5-3-Mosaic

The use of mosaic insecticides also involves a combination of insecticides used herein in a spatial alternation. The insect population of a treated area is subjected to an insecticide, while the population of the adjacent area is subjected to another insecticide.

This strategy is relatively complex to implement and manage in public health because it requires treating villages/neighborhoods with different insecticides. A large-scale trial was conducted in villages in Chiapas, Mexico, against the local malaria vector *An. Albimanus* and was successful [33].

5-4-Getting up area (s) shelter (s)

The delimitation of untreated areas, known as "safe havens", makes it possible to preserve individuals sensitive to insecticides in the direct vicinity of the treated areas. These individuals, not subjected to insecticide treatments, will thus be able to reintroduce regularly sensitive alleles, thus limiting the emergence of resistance and preserving the effectiveness of insecticides. The effectiveness of this type of measure will be strongly influenced by the size of the refuge zone compared to the treated area and the dispersal capacity of the target arthropod species.

This strategy is not feasible in the case of disease vectors for ethical reasons since populations in untreated areas are not protected from pathogen transmission. In places where mosquitoes are not vectors and where treatments are aimed at limiting the nuisance, certain models make it possible to determine an optimal treatment zone that prevents the selection of resistance genes as has been studied in southern France [34]. In practice, this strategy may run counter to the fact that other selection pressures may be exerted in "untreated" areas, such as agricultural or domestic use of insecticides or the presence of pollutants that can reduce the expected efficacy.

Conclusion

Resistance research and monitoring is a prerequisite for the implementation of any vector control program involving the use of insecticidal substances. This monitoring involves an additional cost, to be compared with the expected benefits in terms of the effectiveness and sustainability of vector control programs, anticipation and, consequently, the expected long-term health and economic benefits.

Vector control is only part of the insecticide pressure exerted on arthropod vector populations. The impact of agricultural treatments has been widely documented, and domestic use of insecticides may also interfere with or reduce the effectiveness of vector control. One can also mention the treatments intended to limit the nuisance, which can target the same populations of arthropods but with different objectives. This multiplicity of actors makes it necessary to take into account a holistic approach to vector resistance within a national and inter-ministerial framework.

Based on this finding, recommendations to the various actors involved in vector control with identified priorities in basic and applied research will be of great importance for improving resistance management.

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