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Current Status of the Insecticide Resistance in *Aedes aegypti* (Diptera: Culicidae) from Mexico

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Additional information is available at the end of the chapter

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Abstract

The mosquito *Aedes aegypti* (Diptera: Culicidae) is the primary vector of dengue in Mexico and lately virus Chikungunya, although *Aedes albopictus* is widely distributed; its role in both diseases' transmission has not been confirmed. The control of mosquitoes in Mexico includes source reduction consisting in the elimination of containers that are favorable sites for oviposition and development of the aquatic stage. The use of insecticides is to control larvae and adulticides as outdoor ultra-low volume applications and indoor residual spray and more recently impregnated materials. The health department regulates the use of insecticides, and such regulations are revised and adapted over time. Since 1999, the vector control regulations gave preference to the use of pyrethroids, a permethrin-based formulation to control adult forms. This insecticide was used as the only adulticide in Mexico for more than 10 years. The consequences of this actions have evolved in a widespread and strong resistance to other insecticides, mainly pyrethroids. We include in this revision evidence of resistance reported in *Ae. aegypti* in Mexico.

Keywords: *Aedes aegypti*, pyrethroids, kdr, V1016I, F1534C, Mexico

1. Introduction

Aedes aegypti is the primary urban vector of the viruses causing dengue, Chikungunya, and yellow fever [1–4]. The females are primarily endophagic (feeds indoors) and endophilic (lives indoors) day-biting vectors that feed preferentially on humans [5–7]. They take multiple blood meals before producing an egg batch [8,9], creating the potential for a single infectious female to transmit the virus to more than one person. The females lay their eggs

in containers found in the peridomestic environment, and that is where the immature larvae and pupae develop [10,11]. *Ae. aegypti* is ubiquitous in populated areas of Mexico up to ~1,500 m above sea level [12]. *Aedes albopictus*, which is the primary vector of dengue and Chikungunya viruses, is ubiquitous in rural settings [13–15]. This human biter was introduced into Texas in the 1980s and has spread widely in northern and central Mexico, and the far southern part of the country [16–18].

Urban environments have favored the presence and abundance of *Ae. aegypti* in 30 of 32 states of Mexico (with exception of Tlaxcala and the Federal District) [19–21], and consequently, they have caused the endemic transmission of dengue and more recently, in 2014, of Chikungunya [22].

2. Study area

Mexico is in the southern part of North America, between 14° 32 and 32° 43 North and 86° 42 and 118° 27 West. The country is divided administratively into 31 states and one federal district (Mexico City). Mexico has a land area of 1,964,375 km². It is surrounded by the Gulf of Mexico and Caribbean Sea to the east, the United States of America to the north, the Pacific Ocean to the south and west, and Belize and Guatemala to the southeast. The main features of the physiography of Mexico are Northern and Southern Plateau. Two mountain chains, the Sierra Madre Oriental on the east and The Sierra Madre Occidental on the west, leave plains along the shores of the Gulf of Mexico and the Pacific Ocean. The Sierra Madre Oriental obstructs the circulation of air from the Gulf of Mexico toward Northern and Central Mexico. This characteristic on physiography allows a variety of climates, and the altitude performs a dominant effect on temperature. The prevalent climate conditions are dry to arid in the country. The North territory (47.7%) presents arid and semiarid conditions (23.5%), subhumid with 7 months of long dry season prevailing in Central Mexico, 16.3% presents dry tropical mainly the shores, 12.4% of the territory located in Southern Mexico presents humid tropical climate, and in both mountain chains small areas with humid temperate climate are found [23].

3. The situation of dengue and Chikungunya fever in Mexico

A recent study estimated that up to 390 million dengue virus (DENV) infections, including close to 100 million cases of dengue disease manifestations, occur annually across the world [24]. *Ae. aegypti* and DENV were widely distributed in the Americas in the early 1900s, but a campaign against yellow fever initiated in 1947 and continued to the early 1970s resulted in both the mosquito and its associated viruses being eliminated from most of Central and South America and from Mexico [25]. Success then bred failure as resources were diverted to other health problems. From the 1980s, *Ae. aegypti* has reemerged in the Americas, facilitated by uncontrolled urbanization providing ample opportunities for mosquito breeding and population growth [1,25]. The mosquito now has regained the full extent of its range from a century

ago. This reemergence of the vector combined with global trafficking of DENV in infected humans through increased air travel have led to the Americas becoming hyperendemic, with cocirculation of all four DENV serotypes in many areas [26,27]. In Mexico, dengue reemerged with a DENV-1 outbreak in 1979 followed by outbreaks of the other serotypes in the next two decades [25,28,29]. In 2009, a major dengue epidemic with nearly 250,000 reported clinical cases occurred in Mexico (55,363 confirmed) and this epidemic has continued through 2010 with ~58,000 clinical cases (22,352 confirmed) , 2011 with ~68,000 cases (15,578 confirmed) , 2012 with ~165,000 cases (84,612 confirmed) , 2013 with ~232,000 cases (62,330 confirmed) , 2014 with 125,000 cases (32,100 confirmed), and 2015 (up to September 25, 2015 ~125,000 clinical cases with 13,454 confirmed) [30].

The autochthonous transmission of Chikungunya in the Region of the Americas was first detected on December 2013. By July 2014, an imported case was reported in Mexico, two more imported cases appeared on September 5. By the end of 2014, a total of 131 autochthonous confirmed cases were reported as well as a total of 13 imported cases; and ~7,500 confirmed cases by October 2, 2015 [30].

4. Vector control in Mexico

Since 1950, operational vector control programs in Mexico have used a series of insecticides to control *Ae. aegypti* [31]. The organochlorine insecticide DDT was used extensively for indoor house spraying from 1950 to 1960 and was used in some locations as recently as 1998. In recent decades, the chemical control of mosquito larvae has relied on the use of organophosphate insecticides with temephos as the active ingredient. The adulticide malathion was used for ultra-low volume (ULV) space spraying from 1981 to 1989. An oil-based formulation of chlorpyrifos was registered for use in some locations in Mexico to control the adult stage of the mosquito from 1996 to 1999. The organophosphates as adulticides were replaced by pyrethroids according to the Norma Oficial Mexicana NOM-032-SSA2-2002 [32]. The pyrethroid permethrin was applied as a sole adulticide in Mexico for more than a decade.

On June 1, 2011, a new policy was published in NOM-032-SSA2-2010 [33] that established the characteristics of the insecticides to be used for vector control in Mexico. The selection of the insecticides should be based on vector resistance, effectiveness, and safety related to exposure. The list of insecticides has since been updated each year [34]. A new policy published on April 16, 2015 (NOM-032-SSA2-2014) [35], maintained the same requirements practically as the regulation published in 2011.

5. Insecticide resistance in *Ae. aegypti* – A threat to its control

The extensive use of DDT to control *Ae. aegypti* in Mexico and other parts of the Americas during the 1950s and 1960s resulted in the development of resistance [36]. This action was unfortunate because both DDT and pyrethroids target voltage-gated sodium channels in the

insect nerve sheath where structure-related interactions occur in specific regions of the sodium channels that prolong their opening and produce paralysis. Indeed, the similar mode of action probably produced cross-resistance to pyrethroids in DDT-resistant *Ae. aegypti* [37–41].

Pyrethroid resistance is clearly increasing despite the initial optimism over their rapid action and novelty [42]. Evidence of resistance to permethrin insecticide used in Mexico for more than 10 years in *Ae. aegypti* populations in Mexico due to enzymatic mechanisms such as α - and β -esterases was reported in Baja California North and South [43], in Quintana Roo, south of Mexico [31], and some states of northeast Mexico [44]. More recently, Aponte et al. [45] found increased levels of esterases and glutathione S-transferase related with resistance to DDT, permethrin, and deltamethrin in *Ae. aegypti* populations from the state of Guerrero located on the west coast of Mexico.

The presence of a *kdr* mutation V1016I in the voltage-gated sodium channel gene is also associated with resistance to pyrethroids. This mutation was originally found in a permethrin resistant strain from Isla Mujeres, off the coast of Cancun [46,47]. High frequencies of this resistance allele were subsequently found in collections of *Ae. aegypti* from 78 sites in Mexico with some of the highest frequencies detected in collections from Veracruz state [48,49].

Flores et al. [50] reported an extensive monitoring of the frequency of *kdr* Ile1,016 in *Ae. aegypti* populations from Merida, Yucatan, south of Mexico, as part of the “Casa Segura” project. *Ae. aegypti* collections were characterized by both molecular *kdr* and biochemical resistance to pyrethroid insecticides such as permethrin and deltamethrin. Ile1,016 allele frequencies varied among collection sites ranging from 0.14 to 0.98. Within Merida City, fifteen collection sites had medium to high homozygote frequencies. The lowest Ile/Ile homozygote frequencies corresponded to small towns nearby Merida City.

A second mutation F1534C on the IIS6 domain of the same gene was also detected in *Ae. aegypti* populations from Guerrero state located on the west coast of Mexico [45] and the Yucatan Peninsula [51] conferring resistance to pyrethroids.

The practice of utilizing a single insecticide until the appearance of resistance has become a standard practice that quickly reduces the number of insecticides available for vector control. Rotations, mosaics, and mixtures have instead been proposed as strategies for insecticide resistance management [52–54]. Mathematical models have been applied for estimating how these tools could be used in an optimal manner [55]. However, these models have been rarely tested under field conditions, especially for insect vectors, due to the difficulties in determining changes in frequencies of resistance genes in large samples of insects from resistant populations [56].

In Mexico, there was a large-scale field trial with *Anopheles albimanus* that used rotations or mosaics of insecticides substituting the simple use of DDT or of specific pyrethroids [56,57]. Changes in the frequency of resistance genes were monitored for 4 years [57]. The results were promising and predicted that rotations or mosaics of insecticides are viable long-term strategies for the sustainable use of insecticides in disease control programs.

With that goal in mind [58], the resistance to eight pyrethroids in collections of *Ae. aegypti* from the state of Veracruz located on the east coast of Mexico was examined, considering that this

knowledge would facilitate the selection of viable alternative pyrethroids besides permethrin for use in a rotation program for sustained control of *Ae. aegypti* at the local, regional, and possibly statewide levels. The results obtained showed that the strains analyzed were resistant to δ -phenothrin, deltamethrin, cypermethrin, α -cypermethrin, z-cypermethrin, λ -cyhalothrin, bifenthrin, as well as permethrin and suggested that populations in the state of Veracruz have been exposed to strong selection pressure, resulting from the continuous application of permethrin for more than a decade. They also evaluated resistance to chlorpyrifos [59] in the same strains, and overall, the populations in this study were less resistant to chlorpyrifos than to pyrethroids, so the rotation of insecticides in the control activities is suggested to delay or minimize the occurrence of high levels of resistance to chlorpyrifos among local populations of *Ae. aegypti*.

Saavedra-Rodriguez et al. [60] examined changes in gene expression before, during and after five generations of permethrin laboratory selection in five strains of *Ae. aegypti* collections from the Yucatan Peninsula of Mexico. Changes in expression of 290 metabolic detoxification genes were measured using the *Aedes Detox* microarray. Selection simultaneously increased the LC₅₀, KC₅₀, and Ile1,016 frequency. Ten to eight genes were differentially transcribed after selection, and it was an inverse relationship between the Ile1,016 frequency and the numbers of differentially transcribed genes. Some genes were differential transcribed among field strains, but interestingly a few cytochrome P₄₅₀ genes complex were overexpressed. The authors established that adaptation to permethrin in *Ae. aegypti* laboratory strain is conditioned presumably by geographic origin and extant target site insensitivity in the *para* gene. The lack of uniformity in the genes that responded to artificial selection as well as differences in the direction of their responses challenges the assumption that one or a few genes control permethrin metabolic resistance.

The selection pressure by the prolonged use of pyrethroids in Mexico had resulted in resistance to all of this kind of chemicals recommended for vector control in Mexico. All studies have shown the prevalence of cross-resistance caused by metabolic mechanisms and/or point mutations. Saavedra et al. [51] demonstrated that even in the absence of barriers to gene flow, local insecticide pressure, rather than the migration of mosquitoes with *kdr*-conferring mutations, is the primary determinant of the local *kdr* profile for *Ae. aegypti*. Thus, the early detection of insecticide resistance is highly relevant to establish a rotation program for insecticide resistance management in *Ae. aegypti* in Mexico. In an attempt to establish the importance of evaluating the strength of available techniques to assess the insecticide susceptibility in *Ae. aegypti*, Lopez et al. (in press) conducted a study establishing the intensity of insecticide resistance through the Resistance Intensity Rapid Diagnostic Test (I-RDT) [61]. The RDT-I consists of exposing vector populations 1, 2, 5 and ten times the diagnostic dose previously established at a diagnosis time. For this study, they used four populations of *Ae. aegypti* from the state of Yucatan, south of Mexico, and three population from the state of Nuevo Leon, northeastern Mexico. They were exposed to the diagnostic dose (DD) of permethrin, bifenthrin, and d-(cis-trans)-phenothrin and enhanced DD at 2, 5, and 10 times. All populations resulted resistant to the pyrethroids evaluated according to WHO recommendations for assessing the significance of detected resistance (<90%) even when the DD was enhanced 5

times. To correlate these results with pyrethroid molecular resistance mechanisms, DNA from mosquitoes of each population were used to detect V1016I and F1534C mutations. The allelic frequency of Ile1,016 varied from 0.43 to 0.90 in the populations studied. For the 1534 locus, there was a predominance of homozygous mutant genotype in all populations with high frequencies of the mutant allele (0.75–1), showing that the F1534C mutation was more common than V1016I mutation. They also analyzed the co-occurrence of both V1016I and F1534C mutations, and results showed that more than 50% of mosquitoes genotyped expressed both mutations (double homozygous mutants).

6. Conclusions

The selection pressure exerted by insecticides for more than six decades on the populations of *Ae. aegypti* in Mexico has generated widespread resistance to a variability of insecticides and in the last 15 years to pyrethroids. It is essential that we consider actions to avoid strong resistance between pyrethroids and alternative adulticides. Going forward, strategies must include resistance monitoring, the development of advanced tools for detecting multiple insecticide resistance, and practical tools for efficient vector control.

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