Reducing Dengue Transmission in Mexico in the Face of Increasing Insecticide Resistance

The mosquito *Aedes aegypti* is the primary urban vector of the viruses causing dengue fever. In the absence of preventative vaccines or drugs to treat dengue infections, insecticides are the only immediately available tool for suppression of *Ae. aegypti* populations and subsequent reduction of dengue virus transmission during an outbreak. Because of their safety profile for use around humans, pyrethroids have become the insecticides of choice for *Ae. aegypti* suppression in Mexico and throughout Latin America. Pyrethroids kill mosquitoes by binding to a critical protein expressed on the surface of nerve cells called the voltage gated sodium channel. When a mosquito is exposed to a pyrethroid through sprays, thermal fogs or by contacting treated materials (bed nets, curtains or treated clothing) the pyrethroids rapidly localize to the channel protein and block nerve transmission. Exposed susceptible mosquitoes are immediately "knocked down." Unfortunately, *Ae. aegypti* populations have evolved resistance to pyrethroids through a mechanism known as knockdown resistance (kdr for short). This resistance mechanism involves a change of only one or a few amino acids in the channel protein that reduce the amount and degree of pyrethroid binding.

Over the last few years we, in collaboration with our colleagues at UANL, have documented a rapid rise of kdr-conferring mutations from the late 1990s to present in *Ae. aegypti* in Mexico. We discovered a rapid rise, from 1996-2000 to 2009, of a specific mutation in *Ae. aegypti* from throughout Mexico. The overall frequency of the kdr allele of the channel protein gene have increased from <0.1% in 1996–2000 to 2–5% in 2003–2006, and to 38–88% in 2007–2009 depending upon collection location. For example, in Merida City the mutation was not detected from ~270 *Ae. aegypti* collected in 1999, but the frequency of this mutation had risen to ~50% for 100 specimens collected in 2007 and 75% for >1,200 specimens collected in 2009-2010. Similarly high rates (>70%) of kdr-conferring alleles in 2008-2012 collections of *Ae. aegypti* were reported from multiple other locations in Mexico, islands in the Caribbean, and Brazil. In response to these reports, recommendations by Centro Nacional de Vigilancia Epidemiologica y Control de Enfermedades for insecticide use in vector control in México now include pyrethroid and malathion (an organophosphate) and bendiocarb (a carbamate). These latter two insecticides don't target the channel protein.

Despite this seemingly dire situation, there are three critical weaknesses to kdr in *Ae. aegypti* that Mexico can and should exploit to prolong and possibly sustain the use of pyrethroids. First, only mosquitoes that are homozygous (have 2 copies) for the kdr mutation always survive pyrethroid exposure whereas 10% of heterozygotes (mosquitoes with only one copy of the kdr mutation) are knockdown resistant but ~50% recover following pyrethroid exposure and only individuals homozygous for the regular "susceptible" channel gene are uniformly killed. Second, mosquitoes with kdr may have a lower ability to survive and reproduce. Third, recent field collections with high kdr have been found to have only 8 fold resistance to chlorpyrifos and only 1.8 fold resistance to malathion (both organophospates) and 2.7 fold resistance to bendiocarb. Taken together these weaknesses may suggest a strategy to reduce pyrethroid resistance in *Ae. aegypti*. By rotating among alternative insecticides with different modes of action or different mechanisms of resistance in annual rotations or in spatial mosaic patterns, federal and statewide Mexican control agencies should be able to reduce selection pressure for any one insecticide. In other words they can, even temporarily reduce the use of pyrethroids, but still control *Ae. aegypti* using organophosphates and carbamates then the frequency of kdr will probably decline naturally in the absence of

pyrethroid pressure. Thus if recommendations by Centro Nacional de Vigilancia Epidemiologica y Control de Enfermedades to use alternative insecticides can be implemented on an annual basis or through different insecticides being applied in different locations then there should be a rapid overall decline in kdr. It is certainly worth a try, given the current situation and the lack of viable alternatives.

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