

Susceptibility Status of *Aedes aegypti* to Insecticides in Colombia

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1. Introduction

Dengue is a disease of public health interest for Colombia due to its impact on morbidity and mortality. This disease maintains an endemic behavior in the departments of the country located below 2200 meters above sea level. Between the years 1978 to 2010 it was recorded approximately a number of 1,011,852 cases of dengue in Colombia. Vector populations of *Aedes aegypti* in the country have been continuously pressed for over five decades with insecticides, being the most widely used tool for interrupting transmission of dengue virus during outbreaks and epidemics in the absence of an available vaccine (Figure 1). The selection pressure exercised with these chemicals has led to the emergence of resistant populations of the vector to organochlorine, organophosphate, pyrethroid and carbamate-like molecules.



Fig. 1. Application of insecticides in the home by fogging during outbreaks or epidemics.

The records of vector resistance in the country have increased considerably since 2007 when in Colombia was created the national network for the surveillance of susceptibility to insecticides used in public health to *A. aegypti* and major vector of malaria. With this information a base line has been defined for some Colombian departments in the region and basic knowledge has been generated for decision making from the operating standpoint of vector control programs. However, more research on issues related to the enzymatic mechanisms and molecular causes of resistance in vector populations is required as most results to date have been from diagnostic doses through standardized techniques by the Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO). In this chapter these results are socialized and we discuss some ideas related to the topic.

2. Study area

The continental territory of the Republic of Colombia is located in the northwest corner of South America on the equator. Colombia is located in the north to 12°26'46" north latitude at the place called Punta Gallinas in the peninsula of Guajira. To the south, is located at 4° 12' 30" de latitude south, the East is located at 60°50'54" west longitude from Greenwich, by the West is located at 79°02' 33" west longitude from Greenwich.

Colombia territory also includes the archipelago of San Andres and Providencia in the Caribbean sea between 12° and 16°30' north latitude and 78° and 82° west longitude of Greenwich. Colombia has a land area of 1.141.748 km² ranking fourth among the countries of South America.

Colombia is a country with a wide variety of climates, from the coldest to 0°C to temperatures exceeding 28°C especially in the Caribbean regions, Pacific, Amazon and the Orinoco, accounting for nearly 80% of Colombia territory. Colombia is divided administratively into 32 states, these in turn are divided into 1102 municipalities.

3. The situation of dengue in Colombia

In Colombia, dengue is a disease of public health interest for its impact on morbidity and mortality. Its endemic behavior is due to endemic multiple factors including the re-emergence and intense viral transmission with a rising trend, the behavior of epidemic cycles getting shorter, the increased frequency of outbreaks and serious of the disease, the simultaneous circulation of the four serotypes, infestation by *A. aegypti* in over 90% of the national territory located below the 2,200 meters, and other social factors such as uncontrolled increase and lack of basic sanitation in urban centers (Escobar, 2009). The epidemiological pattern of disease in the last decades has been upward, characterized by exponential increase in endemic areas during the different decades. Cyclical behavior has been characterized by epidemic peaks every three or four years, dealing with the reentry of new serotypes to the country.

In Colombia from 1978 to 2010, has officially been recorded a total of 1.011.852 cases of dengue. For this time period there is record history of the following epidemics in the country:

1977: First recorded epidemic of dengue in Colombia.

2002: Epidemic in 76,996 cases, of which 5269 corresponded to Dengue hemorrhagic fever.

2007: Epidemic in 43,227 cases, of which 4665 corresponded to Dengue hemorrhagic fever.

2010: It is recorded in the country the worst epidemic of this disease with 157,152 confirmed cases and 217 deaths.

The departments that have historically had more transmission of dengue in the country are: Atlántico, Santander, Norte de Santander, Valle del Cauca, Antioquia, Tolima, Huila, Cundinamarca, and Casanare.

4. Resistance to insecticides

4.1 Definition

Resistance is defined as the development of the ability to tolerate doses of toxics, which can be lethal to most individuals in a normal population of the same species and is the result of positive selection pressure exerted by the insecticidal over genes initially in low frequency (WHO, 1957).

4.2 Mechanisms of resistance

The two main resistance mechanisms are alterations in the target site and metabolic resistance, also called increase in the rate of detoxification of insecticides. However, there are other less frequent as there are the resistance behavior and decreased penetration. (Miller, 1988; Bisset, 2002; Fonseca and Quiñones, 2005)

4.2.1 Altered target site

This is generated when no silent mutations occur in structural genes that generate a disturbance of amino acids responsible of anchor of the insecticide at a specific site.

4.2.1.1 GABA Receptor

In bugs this is an hetero multi numeric channel acting as a site of action for cyclodiene and avermectins. The resistance is given by *Rdl* gene (Resistance to dieldrin), which encodes for RDL, a GABA receptor subunit. This type of resistance was first identified in *Drosophila* first identified this type of resistance (Fonseca and Quiñones, 2005).

4.2.1.2 Voltage-gated sodium channel

They are the target of action of pyrethroids and DDT. The sodium para-channel protein is a complex of over 2000 amino acids, composed of 4 homologous domains separated by hydrophilic links, each domain contains six segments. The first mutation in the sodium channel that conferred resistance was detected in *Musca domestica*. subsequently mutations in other insects have been identified including Culicidae resistant to pyrethroids (Martínez et al, 1998; Brengues et al, 2003; Anstead, 2005; Saavedra et al, 2007; Brooke, 2008; Chang et al 2009; Yanola et al, 2010).

4.2.1.3 Insensitive acetylcholinesterase

Insecticide resistance, attributed to Ache insensitivity is found in a number of *Anopheles* and *Culex* species. In general, this mechanism produces a broad spectrum resistance to most organophosphates and carbamates, although more pronounced to carbamates. (Bisset, 2002).

4.2.2 Metabolic resistance

It is conferred by an increase in detoxification insecticide or an inability to metabolize the toxic compound. The most important form of metabolic resistance is given by detoxifying enzymes of the type glutathione S-transferase, mixed function oxidases and esterases (Bisset 2002).

4.2.2.1 Carboxylesterases

They Catalyze the hydrolysis of carboxylic esters and changes in their expression levels, this is the resistance mechanism that occurs most often in insects. In mosquitoes, high levels of these enzymes have been associated with resistance to organophosphate and pyrethroid insecticides (Cui et al, 2007; Rodriguez et al, 2007). Esterases is a family of six proteins

Esterases are a family of six proteins grouped in α and β hydrolases superfamily. In the Diptera these enzymes are encoded by a gene cluster on the same chromosome, each gene may suffer modification that confers resistance to the insecticide (Fonseca and Quiñones, 2005; Santacoloma, 2008).

4.2.2.2 P450 Enzymes or mixed function oxidases

P450 enzymes are encoded by cytochrome P450 genes. P450 enzymes also have other names such as: cytochrome P450 monooxygenases, mixed function oxidases, monooxygenases with polisustrato, microsomal oxidases and heme-thiolate proteins. In insects these enzymes are involved in growth and development through the processing of fatty acids, hormones and pheromones; in the metabolism of secondary plants products and synthetic chemicals such as insecticides. The cytochrome P-450 is implicated as the major factor in many cases of metabolic resistance to carbamates and detoxify organophosphates, pyrethroids and DDT as well. It expresses in tissues of the gut, fat, reproductive tract and Malpighian tubes (Feyerisen, 1999; Poupardin et al, 2008).

4.2.2.3 Glutathione s-transferase

The glutathione s-transferases (GSTs, EC 2.5.1.18) are phase II enzymes involved in xenobiotics detoxification in many organisms. These enzymes metabolize a wide range of toxic hydrophobic compounds such as drugs, insecticides and endogenous toxic substrates, catalyzing the conjugation of glutathione to the hydrophilic center of toxic substances, allowing the increase in compounds solubility. The GSTs are divided into three main groups: the cytosolic, microsomal and mitochondrial. The mitochondrial GSTs have not been found in insects species including mosquitoes. The cytosolic GSTs in insects are grouped into six different kinds: Delta, Epsilon, Omega, Sigma, Theta and Zeta. Most GSTs involved in the metabolism of xenobiotics in insects belong to the class Delta Epsilon. GSTs in insects have been implicated in the insecticide resistance through its direct metabolism, sequestration or protection against secondary toxic effects such as increased lipid peroxidation induced by exposure to insecticides. Glutathione S- transferase mediated detoxification has been reported for insecticides of the organophosphate type and DDT. The main role of GSTs in the resistance to organophosphates is the detoxification of the insecticide by a conjugation reaction. The specific GSTs also catalyze the metabolism of DDT to a non-toxic substance: 1,1-dichloro-2,2-bis-(p-chlorophenyl) ethane (DDE), through the process of dehydrochlorination. Epsilon class of GST has been involved in resistance to DDT in *Anopheles gambiae* and *A. aegypti* (Lumjuan et al, 2007).

4.3 Type of resistance

4.3.1 Cross resistance

It occurs when a single gene confers resistance to a number of chemicals in the same group, as it is the case of phosphotriesterases that provides resistance to several organophosphates or *kdr* gene that confers resistance DDT and the pyrethroids (WHO, 1957).

4.3.2 Multiple resistance

It occurs when two or more resistance mechanisms are operating in the same insect. The multiple resistance term does not necessarily involve the term cross-resistance, because a bug may be resistant to 2 or more insecticides and each resistance can be attributed to different mechanisms (Bisset, 2002).

4.4 Techniques used to detect resistance insecticides in mosquitoes

4.4.1 Biological test of the World Health Organization (WHO)

Technique standardized by the World Health Organization (WHO). In adult mosquitoes the technique consists of exposing individuals of the populations we intent to evaluate to papers impregnated with a single and specific dose of an insecticide during a determined time (1 hour with the exception of the organophosphate fenitrothion, to which will be exposed for 2 hours). The mosquitoes are then transfered to a paper that hasn't been impregnated, where they rest under controlled conditions of temperature, relative humidity and an energy source consisting of a sugar solution (Figure 2A). The mortality reading is done after 24 hours of exposure to the insecticide (WHO 1981a).

The susceptibility of larvae is measured by exposing individuals to a diagnostic concentration or several temephos concentrations to determine the lethal concentration (LC_{50} or CL_{95}) to calculate resistance factor using water as solvent (Figure 2B). Individuals remain exposed for 24 hours. (WHO 1981b) (Santacoloma, 2008).



Fig. 2A. Biological test of the World Health Organization (WHO) (mosquitoes).

4.4.2 Test for biological control center and prevention (CDC)

The impregnated bottles technique was standardized by the Center for Diseases Control and Prevention (CDC) (Brogdon and McAllister, 1998). The objective of this technique is to measure the time it takes dose of an insecticide to reach the target site of action in the



Fig. 2B. Biological test of the World Health Organization (WHO) (Larvae).

mosquito. Involves subjecting a sample of mosquitoes between 15 and 25 individuals of the population to be evaluated on a glass surface pre-impregnated with the dose of insecticide. (Santacoloma, 2008) (Figure 3).



Fig. 3. Test for biological control center and prevention (CDC).

4.4.3 Synergists

These are chemicals that specifically inhibit insecticide-metabolizing enzymes, enhancing their action. Among the synergists more used to detect resistance mechanisms in Insects are the S, S, S - tributylfosforotioato (DJF) and esterases inhibitor and of the enzyme glutathione transferase (GST), the triphenyl phosphate (TFF) specific esterase inhibitor, piperonyl butoxide (PB), an inhibitor of monooxygenases, and ethacrynic acid (EA), a specific inhibitor of the enzyme glutathione transferase (GST) (Rodríguez, 2008).

4.4.4 Biochemical test

The biochemical assays are used to define metabolic mechanisms that may be responsible for the physiological resistance in an insect population (WHO, 1992). The metabolic mechanisms include tests to determine the target enzyme decreased sensitivity or the increased enzyme activity. For the first mechanism in particular, measures the change in acetylcholinesterase associated with resistance to carbamates and organophosphates. For the second, evaluates the increased activity of esterases, mixed function oxidases and glutathione s-transferase for kidnapping or increased detoxification of insecticides (Santacoloma, 2008).

4.4.5 Molecular tests

These tests consist in the amplification of specific gene sequences through polymerase chain reaction technique (PCR) to detect mutations.

4.5 Current state of susceptibility to insecticides *Aedes aegypti* in Colombia

Since the late forties, when first reported resistance to DDT in *Aedes tritaeniorhynchus* (Weidemann) and *Aedes sollicitans* (Walker) resistance has been recorded in over a hundred species for one or more insecticides of public health use worldwide (Brown, 1986; Fonseca & Quiñones, 2005). For *A. aegypti* in America resistance has been reported to organochlorines, organophosphates, pyrethroids and carbamates in Argentina, Brazil, Mexico, El Salvador, Peru, Panamá, Venezuela, Cuba, Puerto Rico, among other Caribbean countries, whose resistance mechanism in some of these stocks has been associated with altered levels of alpha esters, beta esterases, mixed function oxidases, glutathione s- transferase, as well as mutations in the voltage-gated sodium channel. (Rawlins, 1998; Bisset et al, 2001; Brengues et al, 2003; Macoris et al, 2003; Aparecida et al, 2004; Rodríguez et al, 2004; Chavez et al, 2005; Flores et al, 2005; Pereira da-Cunha et al, 2005, Alvarez et al, 2006, Pereira-Lima et al, 2006; Beserra et al, 2007; Saavedra et al, 2007; Bisset et al, 2009; Martins et al, 2009; Albrieu-Llinas et al, 2010; Polson et al, 2010).

Colombia has applied insecticides for control of vector insects for over five decades. The DDT was the first applied to control malaria and during the campaign for the eradication of *A. aegypti* conducted in the early 1950. This insecticide was banned in the late 60's, due to the findings of resistance worldwide (Brown, 1986). Since 1970, organophosphates including temephos were applied and from the early 90's the use of pyrethroids was started. From that time on, the country has been rotating the application of molecules for mosquito control such as: deltamethrin, lambda-cyhalothrin, malathion, fenitrothion and in the last three years cyfluthrin and pirimiphos-methyl. However, the resistance to these insecticides has been documented gradually, making it difficult to take control actions within programs of Vector Borne Diseases in different regions of the country.

In Colombia until the 1990's there were few works assessing the state of susceptibility in Culicidae populations of interest in public health. Between 1959 and 1987 the first cases of DDT resistance were registered in populations of *Anopheles albimanus* (Wiedemann) in the municipalities of El Carmen (Bolívar); Codazzi, Robles and Valledupar (Cesar); Acandí (Chocó) and *An. darlingi* (Root) in some locations of Quibdó municipality (Chocó) (Quiñones et al, 1987). Later Suarez et al, (1996) recorded in the 90's decade the first case of resistance to temephos in the *A. aegypti* species in Cali, Valle del Cauca, and Bisset et al, (1998) evaluated the susceptibility in a strain of *Culex quinquefasciatus* (Say) from Medellín, Antioquia, encountering resistance to organophosphates malathion, primifos-methyl, chlorpyrifos, temephos, fenthion and pyrethroids deltamethrin and permethrin.

In the absence of enough studies in Colombia on susceptibility status of populations of *A. aegypti* to several insecticides of use in public health and in compliance with public policies enshrined in the American continent resolutions CD39.R11 1996, CD43R4 2001 of the Pan American Health Organization, during the years of 2005 and 2007 a national project was conducted, this was funded by Colciencias (Colombian Science and Research Organization) and implemented by the Learning and Control of Tropical Diseases Program (PECET) of the University of Antioquia, the International Centre for Training and Medical Research (CIDEIM), the National University in Colombia, the National Institute of Health (NIH) and 12 departments of health seeking to generate baseline susceptibility of vector populations in Colombia. This multicentered project gave rise to the national surveillance network susceptibility to insecticides for *A. aegypti* and main vectors of malaria led by the National Institute of Health (INS). Since then the record of resistance to *A. aegypti* in Colombia expanded through biological tests by the CDC and WHO as well as the determination of impairment of enzymes involved in resistance.

With these results it has been observed for Colombia widespread resistance to DDT (Figure 4A-4B) and variability in susceptibility to the following insecticides: temephos, lambda-cyhalothrin, deltamethrin, permethrin, cyfluthrin, etofenprox, malathion, fenitrothion, pirimiphos methyl, bendiocarb and propoxur in different regions, with deterioration in some populations in the levels of nonspecific esterases, mixed function oxidases and in smaller proportion to glutathione s-transferases (Figure 5A, 5B, 5C, 5D) (Rojas et al, 2003; Cadavid et al, 2008; Fonseca et al, 2006; Fonseca et al, 2007; Orjuela et al; 2007, Salazar et al, 2007; Santacoloma et al, 2008; Fonseca et al, 2009; Maestre et al, 2009; Maestre et al, 2010; Ardila and Brochero, 2010, Gomez et al, 2010; Maestre et al, 2010, Fonseca et al, 2011).

For temephos resistance has been observed in Cundinamarca, Guaviare, Meta, Santander, Cauca, Valle del Cauca, Nariño, Huila, Caldas, Sucre, Atlántico, La Guajira. (Anaya et al, 2007; Santacoloma, 2008; Maestre et al, 2009; Ocampo et al, 2011) (Figure 6).

Pyrethroids that despite being used in Colombia more recently compared to organophosphates, have shown higher levels of resistance despite the increased use time of organophosphate (Figures 7A, 7B, 7C, 7D, 7E), (8A, 8B, 8C). Among the pyrethroids lambda is the insecticide which displays higher frequency of resistance in vector populations in the country. However, there are pyrethroids such as permethrin and etofenprox that despite having no use in public health have resistance generated in populations of *A. aegypti* from Casanare, Antioquia, Chocó and Putumayo (Ardila and Brochero, 2010; Fonseca et al, 2011).

For the carbamate propoxur discordance in susceptibility results was observed between the WHO technique in which resistance and CDC susceptibility is recorded. Further studies are required to determine the state of populations' susceptibility to the insecticide (Fig. 9 AB). Furthermore, few studies in the country have evaluated the susceptibility of the vector to the

insecticide Bendiocarb to which there has been resistance registered in the populations in the department of Cauca, Valle del Cauca, Huila and Nariño (Figure 10 AB) (Ocampo et al, 2011). Currently it has not been registered for the country mutations in voltage-gated sodium channel gene. It is therefore recommended studies to perform studies to explain resistance observed to most of the pyrethroids evaluated in different country populations and may be related to a crossed resistance to DDT. It is also recommended to perform studies to determine cross resistance to other molecules such as organophosphate and carbamate, as well as multi resistance studies.

For Colombia it is recommended to maintain a system of permanent time and space surveillance that allows health authorities to use insecticides with technical criteria to maintain effective control interventions in vector populations.



Fig. 4A. Susceptibility status of *Aedes aegypti* populations to DDT in Colombia (CDC test).



Fig. 4B. Susceptibility status of *Aedes aegypti* populations to DDT in Colombia (OMS test).

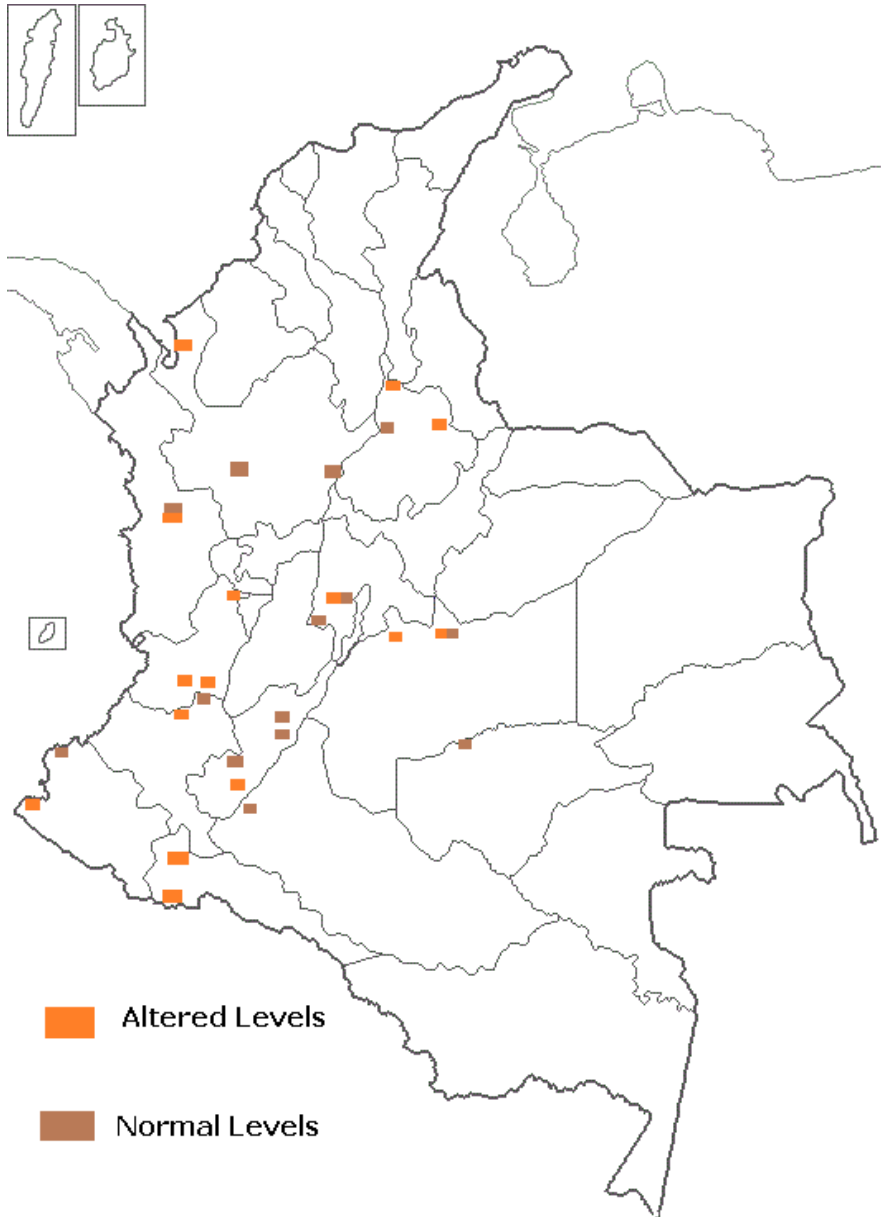


Fig. 5A. Non-specific esterases (NSE).



Fig. 5B. Mixed-function oxidases (MFO).



Fig. 5C. Glutathione-S-transferases (GST).



5D

Fig. 5. Biochemical mechanism of resistance in population of *Aedes aegypti* in Colombia: Non-specific esterases (NSE) (5A); Mixed-function oxidases (MFO) (5B); Glutathione-S-transferases (GST) (5C); acetylcholinesterase (AChE) (5D).

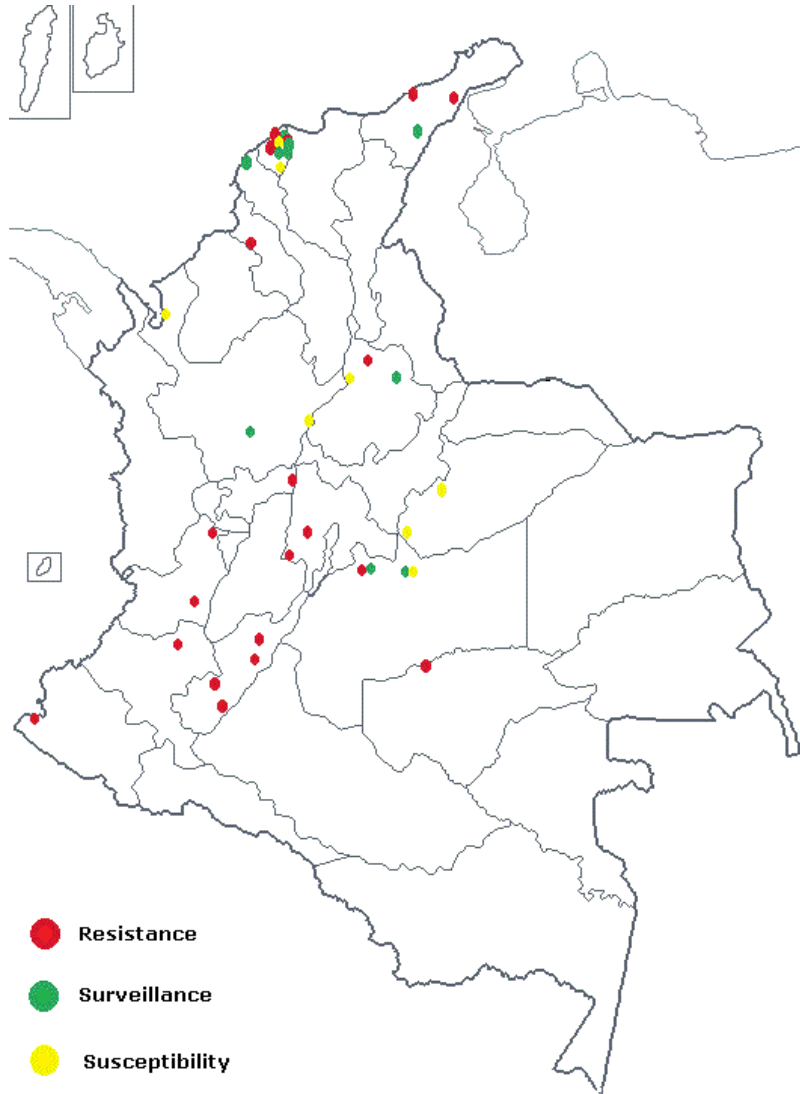


Fig. 6. Susceptibility status of *Aedes aegypti* populations to Temephos in Colombia (OMS test).

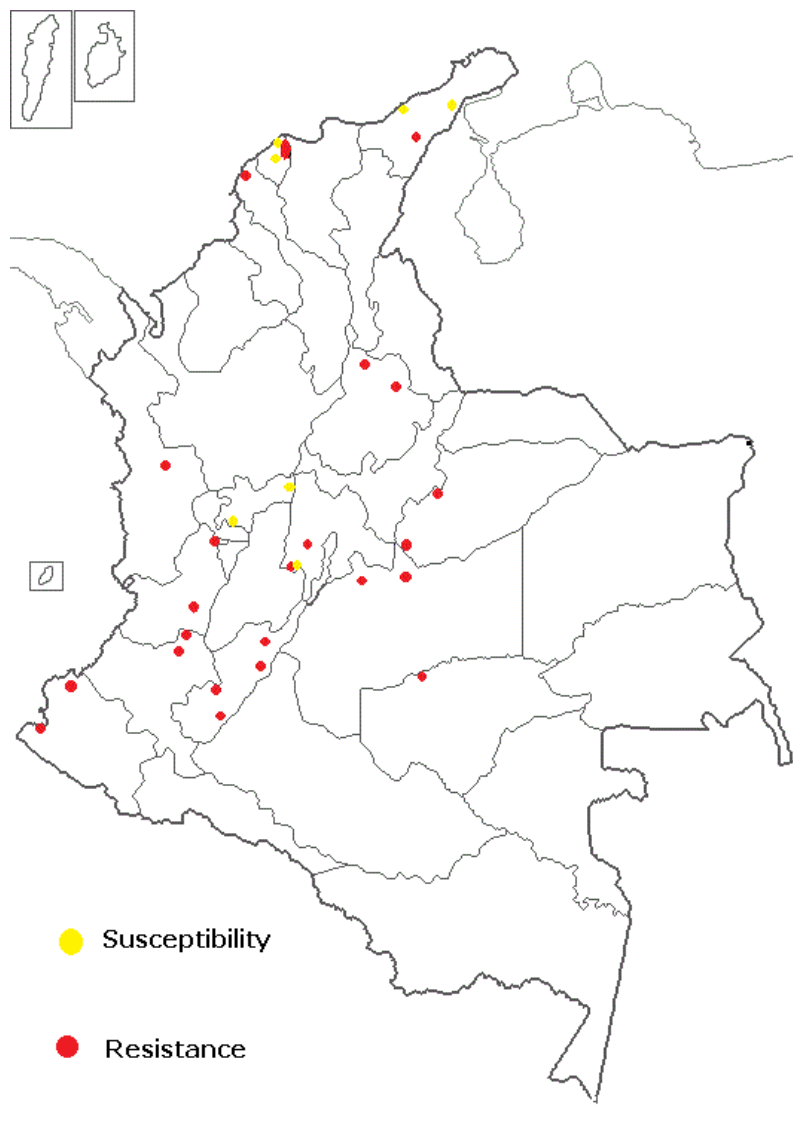


Fig. 7A. Susceptibility status of *Aedes aegypti* populations to lambda-cyhalothrin in Colombia (CDC test).

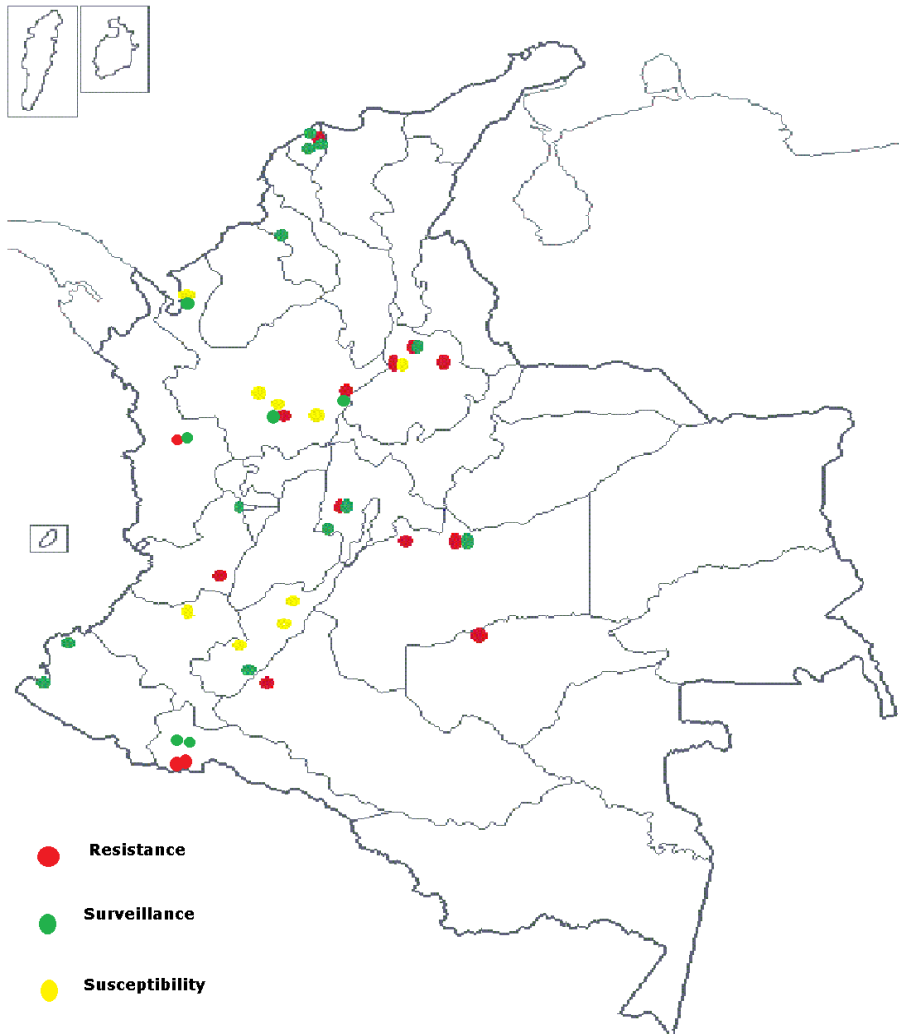


Fig. 7B. Susceptibility status of *Aedes aegypti* populations to lambda-cyhalothrin in Colombia (OMS test).

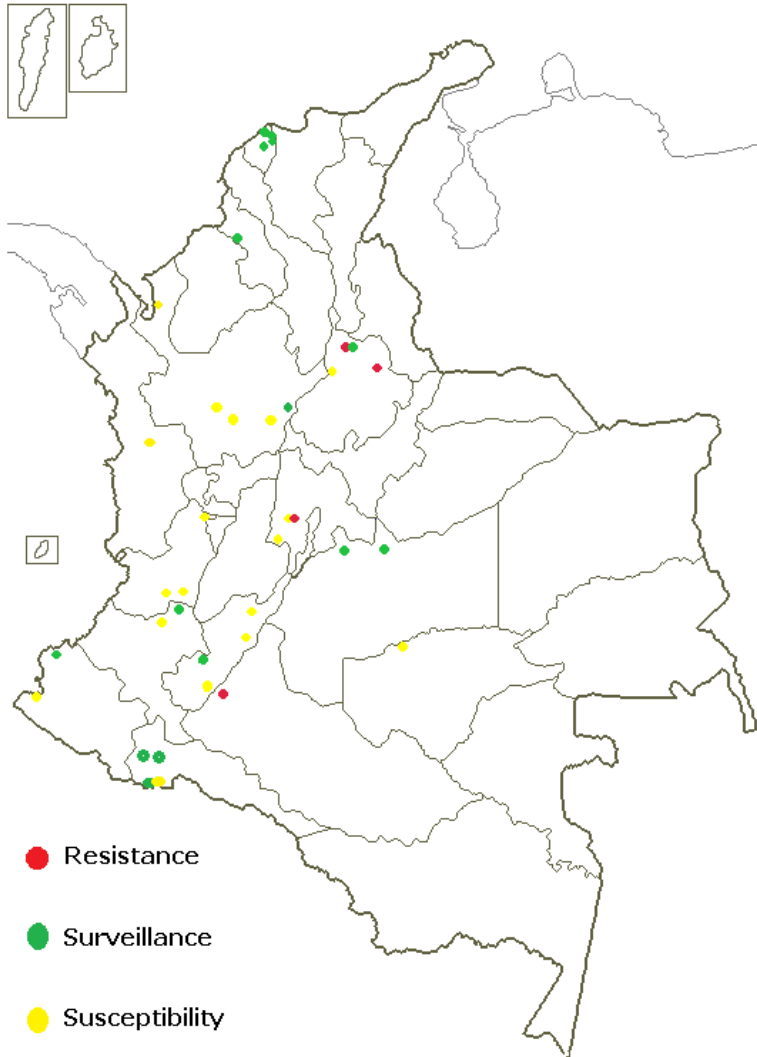


Fig. 7D. Susceptibility status of *Aedes aegypti* populations to Deltamethrin in Colombia (OMS test).

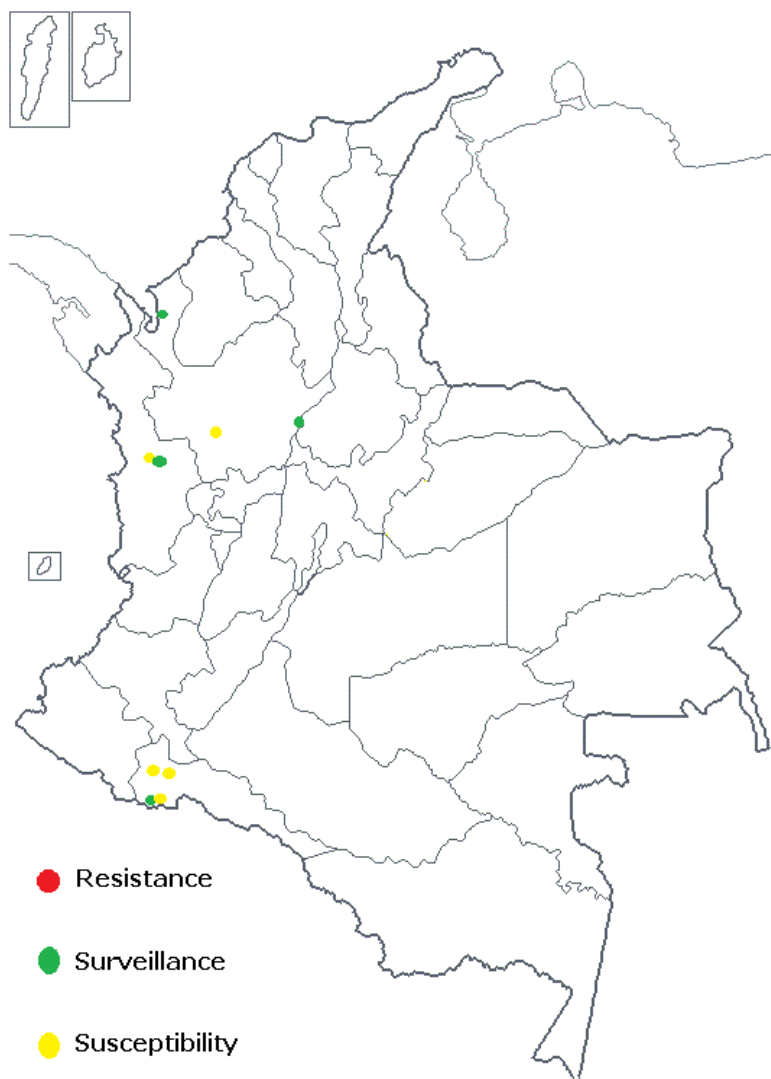


Fig. 7F. Susceptibility status of *Aedes aegypti* populations to cyfluthrin in Colombia (OMS test).

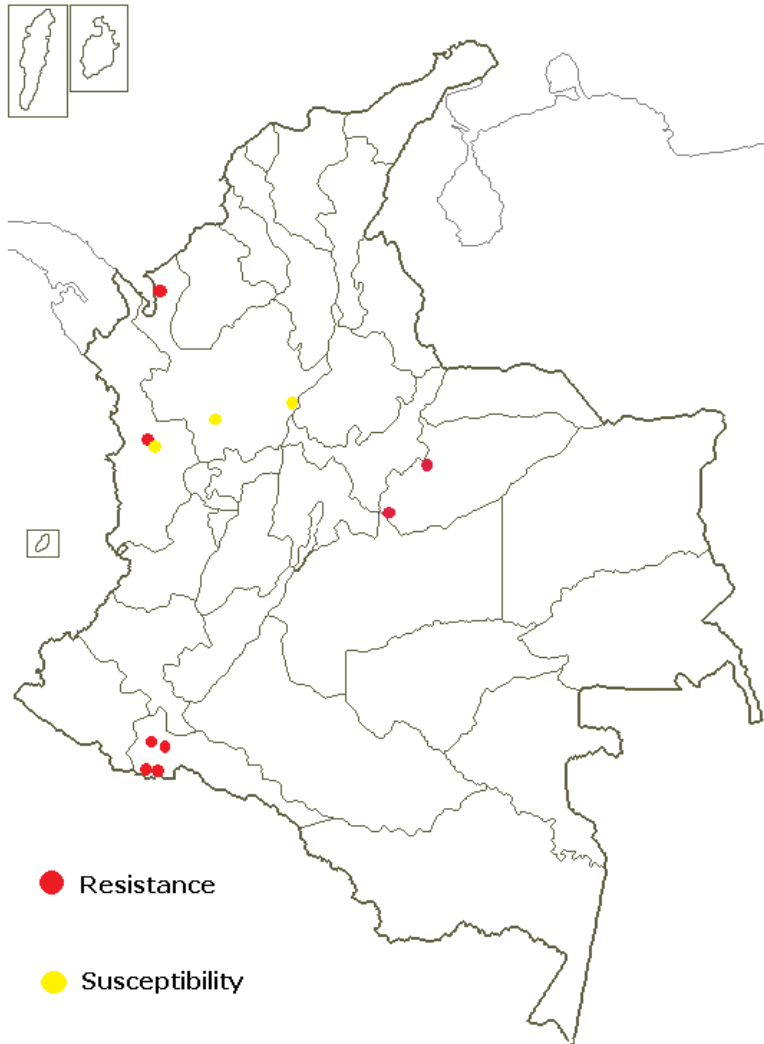


Fig. 7G. Susceptibility status of *Aedes aegypti* populations to Permethrin in Colombia (CDC test).

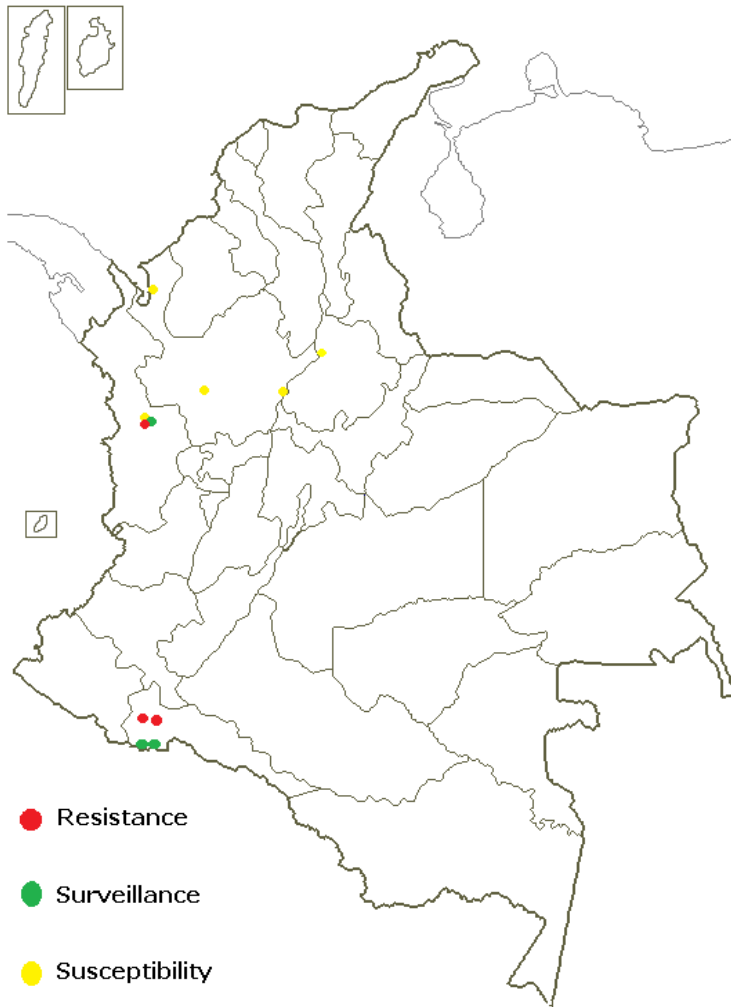


Fig. 7H. Susceptibility status of *Aedes aegypti* populations to Permethrin in Colombia (OMS test).



Fig. 7I. Susceptibility status of *Aedes aegypti* populations to etofenprox in Colombia (OMS test).

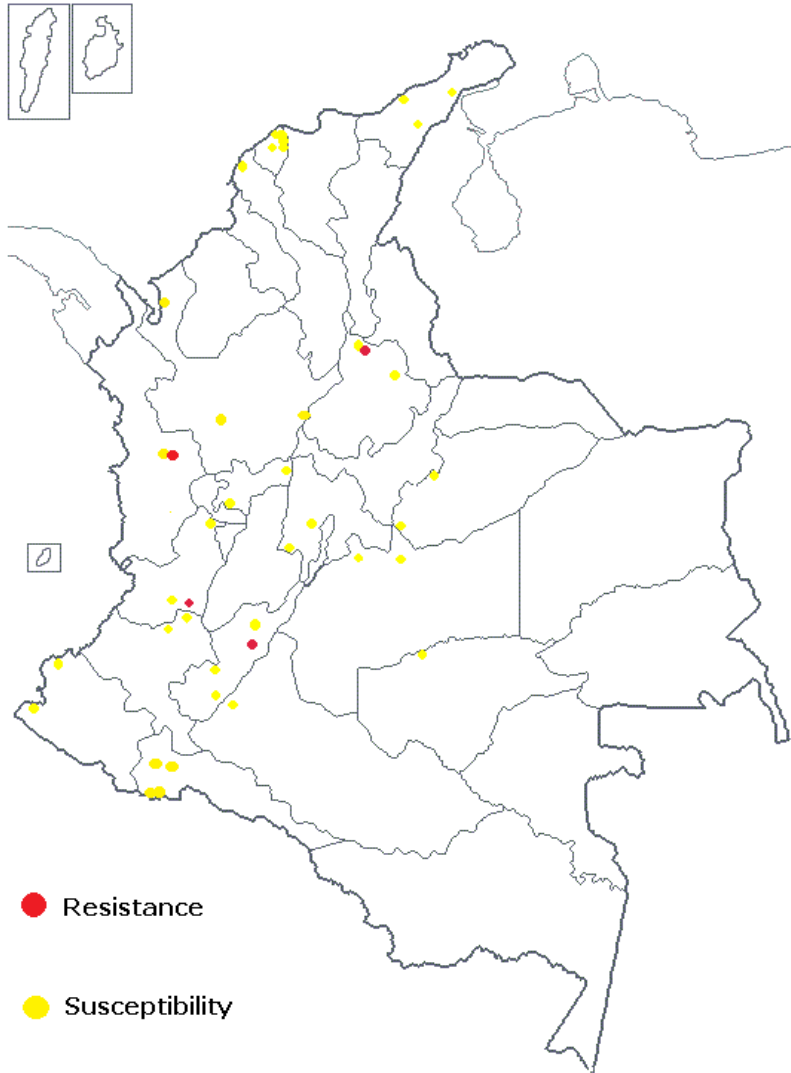


Fig. 8A. Susceptibility status of *Aedes aegypti* populations to Malathion in Colombia (CDC test).

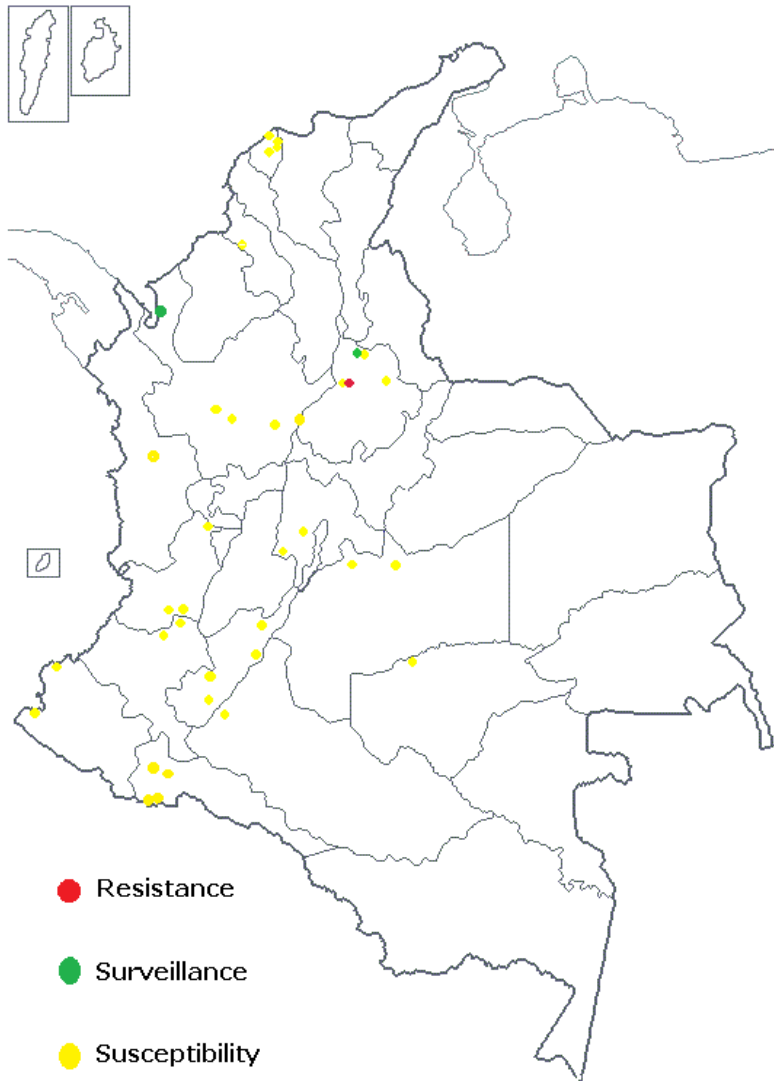


Fig. 8B. Susceptibility status of *Aedes aegypti* populations to Malathion in Colombia (OMS test).



Fig. 8C. Susceptibility status of *Aedes aegypti* populations to Fenitrothion in Colombia (CDC test).

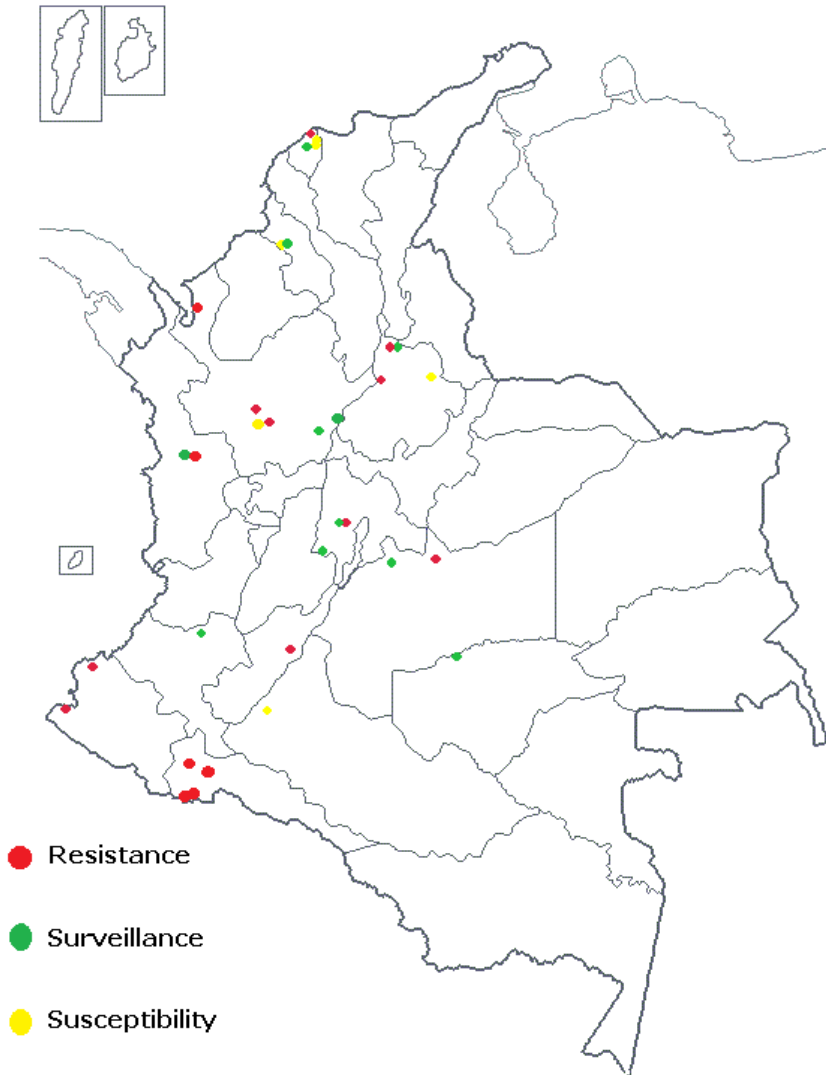


Fig. 8D. Susceptibility status of *Aedes aegypti* populations to Fenitrothion in Colombia (OMS test).



Fig. 8E. Susceptibility status of *Aedes aegypti* populations to pirimiphos methyl in Colombia (CDC test).

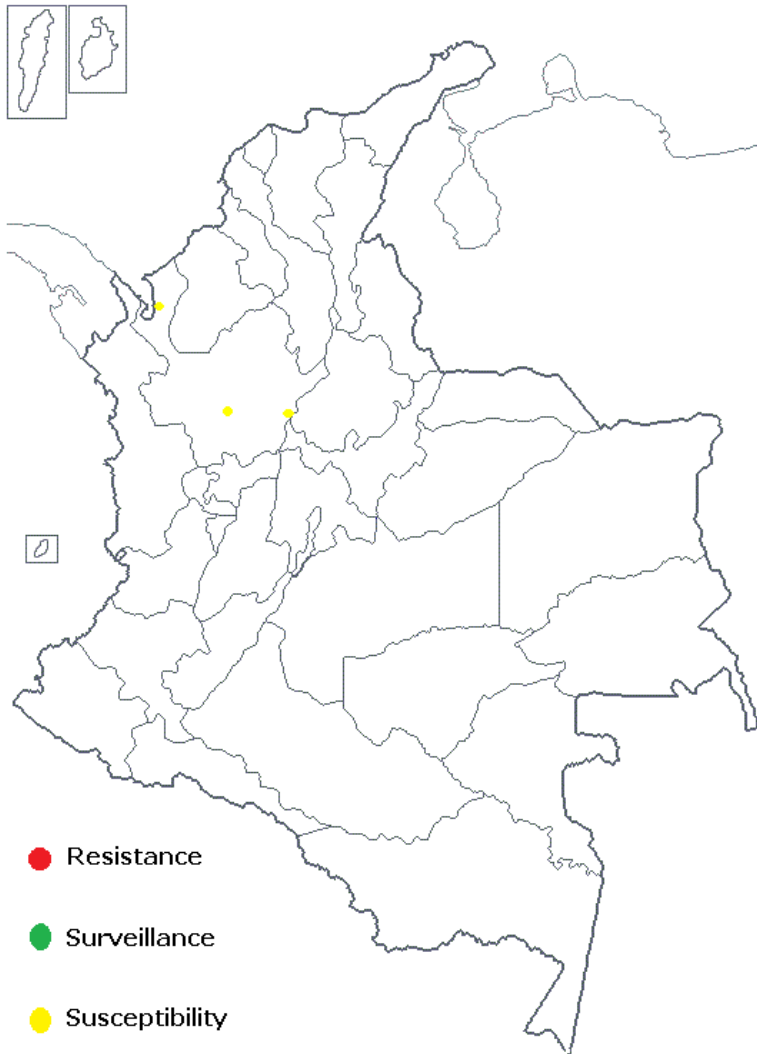


Fig. 8F. Susceptibility status of *Aedes aegypti* populations to pirimiphos methyl in Colombia (OMS test).

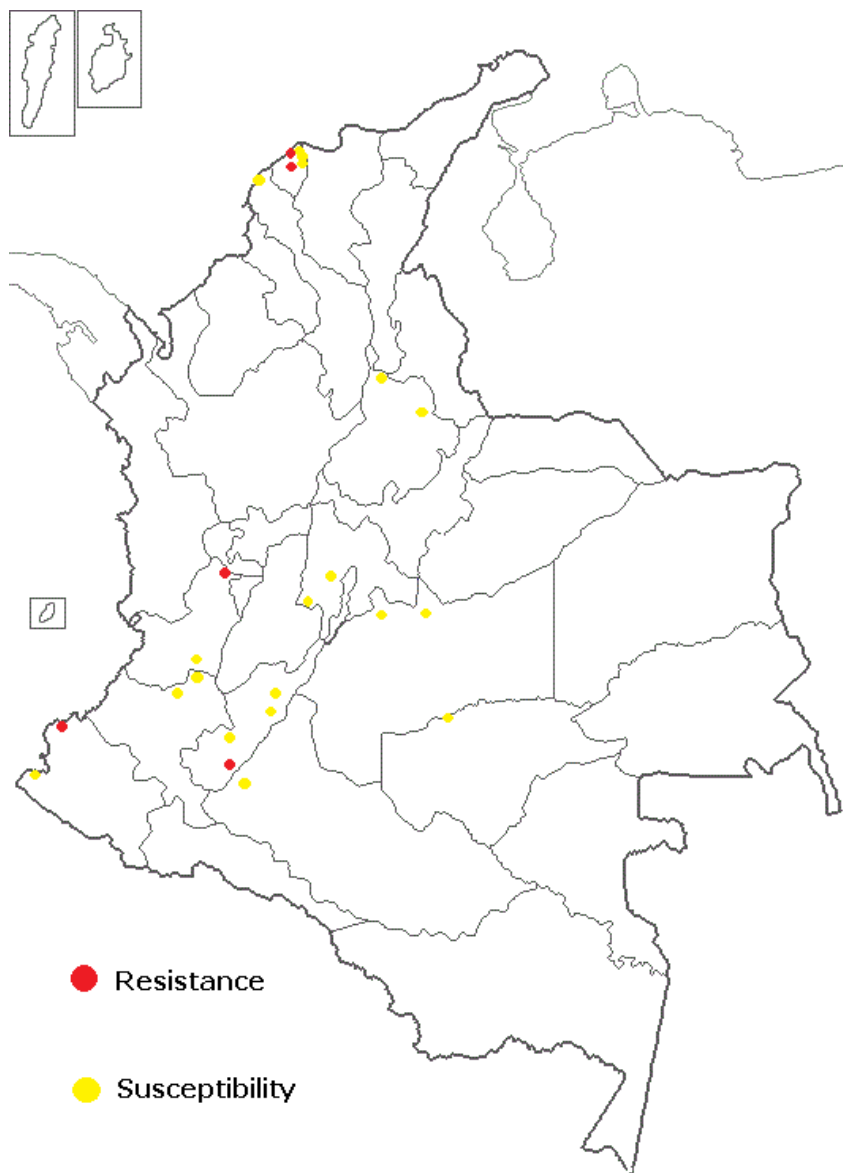


Fig. 9A. Susceptibility status of *Aedes aegypti* populations to propoxur in Colombia (CDC test).

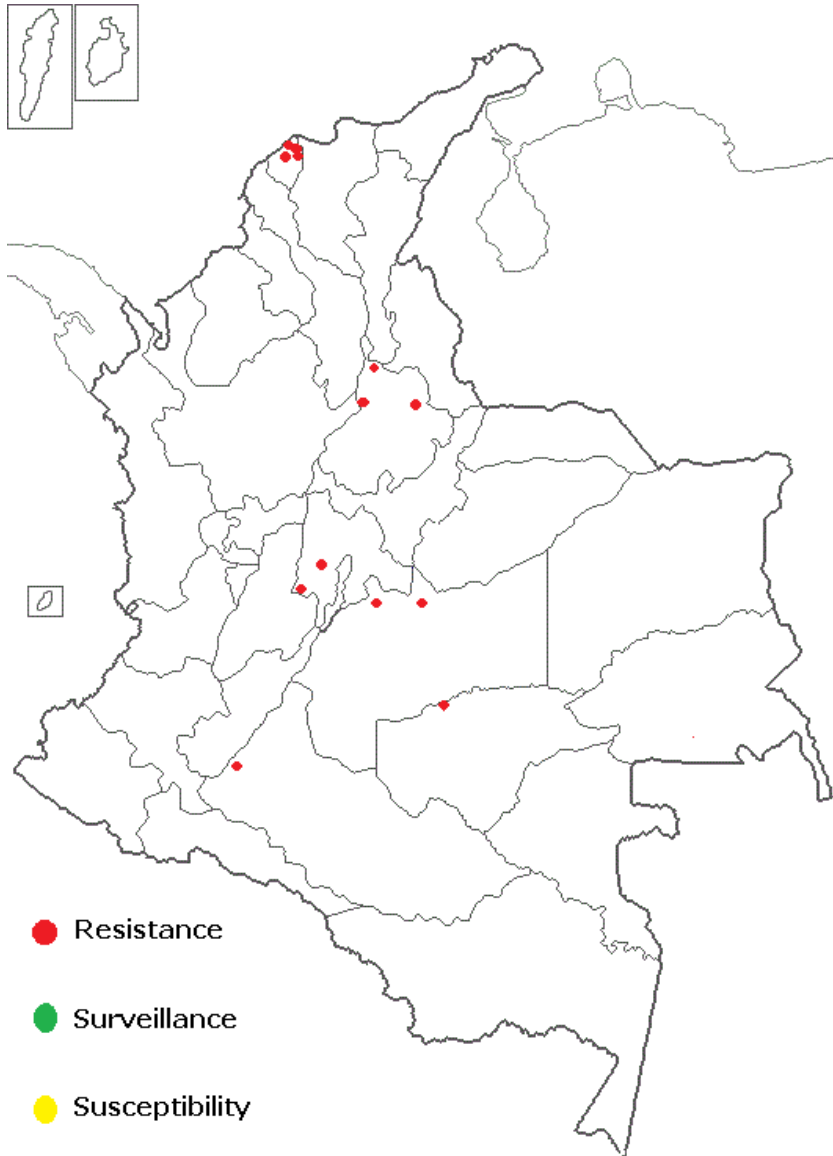


Fig. 9B. Susceptibility status of *Aedes aegypti* populations to propoxur in Colombia (OMS test).



Fig. 10A. Susceptibility status of *Aedes aegypti* populations to bendiocarb in Colombia (CDC test).



Fig. 10B. Susceptibility status of *Aedes aegypti* populations to bendiocarb in Colombia (OMS test).

5. Conclusion

The selection pressure exerted by insecticides for more than five decades on the populations of *A. aegypti* in Colombia, has generated widespread resistance to DDT and variability in susceptibility to phosphorated, carbamates and pyrethroids insecticides. As a possible cause of metabolic resistance to these insecticides, alteration in nonspecific esterase levels has been registered, mixed function oxidases and s-glutathione transferases. However, it is unknown whether there are alterations in target sites of action, especially in voltage-dependent sodium channel genes that explains the generalized resistance to DDT and most pyrethroids in the country.

6. Acknowledgment

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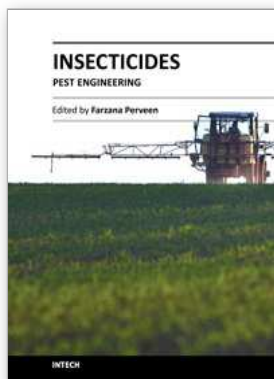
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This book is compiled of 24 Chapters divided into 4 Sections. Section A focuses on toxicity of organic and inorganic insecticides, organophosphorus insecticides, toxicity of fenitrothion and permethrin, and dichlorodiphenyltrichloroethane (DDT). Section B is dedicated to vector control using insecticides, biological control of mosquito larvae by *Bacillus thuringiensis*, metabolism of pyrethroids by mosquito cytochrome P40 susceptibility status of *Aedes aegypti*, etc. Section C describes bioactive natural products from sapindaceae, management of potato pests, flower thrips, mango mealy bug, pear psylla, grapes pests, small fruit production, boll weevil and tsetse fly using insecticides. Section D provides information on insecticide resistance in natural population of malaria vector, role of *Anopheles gambiae* P450 cytochrome, genetic toxicological profile of carbofuran and pirimicarb carbamic insecticides, etc. The subject matter in this book should attract the reader's concern to support rational decisions regarding the use of pesticides.

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