Review

Chemical control of *Aedes aegypti*: a historical perspective

Control Químico de *Aedes aegypti*: Una Perspectiva Histórica

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ABSTRACT

Objective: To describe the use of chemical insecticides throughout history as the main tool to fight against *Aedes aegypti*, a vector of dengue virus.

Methods: A text mining approach was conducted on databases, such as PUBMED and SCIENCE DIRECT, using the keywords "*Aedes aegypti*", combined with the words "insecticides", "resistance", "organochlorines", "organophosphates", "carbamates" and "pyrethroids". Results related to historical information dealing with the chemical control of *Aedes aegypti*, in particular those containing data on insecticide resistance for this species, were scrutinized and analyzed.

Results: Different chemical groups have been developed to control *A. aegypti*, including organochlorine, organophosphate, carbamate and pyrethroid insecticides. In general, the tendency has been to replace a particular pesticide, for which resistance had been detected, for a new one, mosquito-sensitive, and with little evidence of deleterious effects derived from its use. The spread of resistance has been registered in several countries of America, Asia and Africa. Two mechanisms have been highly cited to be responsible for the resistance; the increase activity of detoxifying enzymes, and structural changes in the insecticide target site, mostly within the central nervous system.

Conclusion: Excessive use of chemical insecticides and the lack of dosing control have led to widespread resistance in *A. aegypti*, as no "safer" alternative chemical options are available for vector control in different countries, impacting human health.

Keywords: *Aedes*, Vector Control, Insecticide Resistance, Toxic Substances. (source: MeSH/NLM).

RESUMEN

Objetivo: Describir el uso de insecticidas químicos a través de la historia como la principal herramienta contra *Aedes aegypti*, un mosquito vector del virus del dengue.

Métodos: Una búsqueda en minería de textos fue realizada en bases de datos como PubMed y Science Direct, utilizando las palabras clave "*Aedes aegypti*", en combinación con "insecticidas", "resistencia", "organoclorados", "organofosforados", "carbamatos" y "piretroides". Resultados afines con la información histórica relacionada con el control químico del mosquito *Aedes aegypti*, en particular las que contienen datos sobre la resistencia a insecticidas de esta especie, fueron examinados y analizados.

Resultados: Diferentes grupos químicos han sido desarrollados para el control de *Aedes aegypti*, incluyendo organoclorados, organofosforados, carbamatos y piretroides. En general, la tendencia ha sido la de sustituir un pesticida particular, para el que ha sido detectado resistencia, por uno nuevo, mosquito-sensible, y con evidencia de efectos perjudiciales derivados de su uso. La propagación de la resistencia se ha registrado en varios países de América, Asia y África. Dos mecanismos han sido altamente referenciados de ser responsable de la resistencia, el aumento de actividad de las enzimas de desintoxicación, y los cambios estructurales en el sitio de destino de los insecticidas, en su mayoría dentro del sistema nervioso central.

Conclusión: El uso excesivo de insecticidas químicos y la falta de control de dosificación han dado lugar a una resistencia generalizada en *A. aegypti*, y alternativas químicas "más seguras" no están disponibles para el control de vectores en diferentes países, afectando la salud humana.

Palabras claves: *Aedes*, Control de Vectores, Sustancias Tóxicas. (fuente:DeCS/BIREME).

Aedes aegypti (Diptera: Culicidae) is the mosquito responsible for the transmission of dengue in tropical and subtropical regions of the world (1, 2), including the South Pacific, Southeast Asia, India, Africa and the subtropical zone of America (3). This vector is distributed between 35° North and 35° South, but it may extend to 45° North to 40° South. Usually, it is found below 1200 m, although it has been reported around 2400 m (4). *A. aegypti* is native to Africa and it probably invaded other continents via transport ships that carried freshwater reservoirs on board, and resupplied in African ports during the fifteenth through seventeenth centuries, being introduced into the rest of the world following the same route (5). Breeding sites are essentially artificial: urban (vacant lots, salvage yards, landfills) or domestic (tires, bottles, open cans or containers of any kind, drinking water, tanks, pots and jars, among others) (4).

Over the last 25 years there has been a global increase in both the distribution of *A. aegypti* and the epidemic dengue virus activity (5). It has been estimated that worldwide, 2.5 billion people are at risk of acquiring the disease, approximately 50–100 million cases of dengue fever are reported each year, 500,000 people with severe dengue require hospitalization, and around 2.5% of diseased people die (6). The expansion of the mosquito populations may be explained by many factors, including demographic explosion, global warming, and the traffic of people between the infested communities and those previously vector free (7).

The control of *Aedes* populations is performed using several strategies, such as environmental management, chemical, biological and integrated control. The first is the most effective, preventing or reducing the breeding of mosquitoes and human-vector pathogen contact. Environmental management is focused on the destruction, alteration, disposal or recycling of containers, and natural larval habitats, that produce the greatest number of adult *Aedes* mosquitoes in each community. These activities are concurrently developed with health education programs, utilizing communication strategies that encourage community participation in the planning, execution, and evaluation of container–management programs. Three types of environmental management programs have been defined: first, environmental modification based on long lasting physical transformations of vector habitats; second, environmental manipulations, aimed to generate temporary changes to vector habitat, as a result of planned activity to produce unfavorable conditions to vector breeding; and third, changes in human habitat or behavior (8). However, the most widely used control for *Aedes* populations, due to its effectiveness in regulating larval and adult populations, is the utilization of chemical insecticides (9).

There are three methods of applying chemical control. Larvicide application or focal control, used to treat household drinking water containers, has low, relative toxicity, and is safe for humans. Another method is perifocal treatment, which utilizes sprinklers in larval habitats and destroys not only larvae but also adult mosquitoes. Finally, space spraying is generally employed in emergency outbreaks of dengue (8). It is important to emphasize that larvicides should be considered as a complementary method to environmental management and those are intended to impact the mosquito density and longevity, as well as other transmission parameters. Another strategy is biological control, which introduces predators or parasites to compete or reduce the populations of the target species. Larvivorous fish and the biocide *Bacillus thuriengensis* H -14 (BTI) are the two most frequently employed organisms. According to McCall and Kittayapong (10), the pyriproxyfen, and insect growth regulator, has also been used for the control of the dengue vector. This method has been documented for the immature stages of the vector mosquitoes (11). Finally, integrated control is the combination of the available control methods in the most effective, economical, and safe manner to decrease vector populations (8).

As chemical insecticides have been the most important tools employed for the management of dengue vector mosquito, the objective of this review was to describe those pesticides that have been used throughout history in the control of *Aedes aegypti*.

METHODS

This paper consists of a thematic review that was done searching in databases such as PUBMED, SCIENCE DIRECT, books, and webpages of public health organizations from several countries, including as well the World Health Organization and Panamerican Health Organization. Keywords as “chemical insecticides”, “*Aedes aegypti*”, “resistance”, “organochlorines”, “organophosphates”, “carbamates” and “pyrethroids”, were employed to carry out the search. Aspects such as the history of chemical insecticide use, resistance development, resistance mechanisms, and effects of pesticides on human health, constituted the inclusion criteria to consider citations in the review.

RESULTS

Evolution of mosquito control with chemical insecticides

Initially, insect control was carried out with natural products, but the development of chemical insecticides slowed down basic research on this issue (12). Throughout history, four common classes of chemical insecticides have been used to control *A. aegypti*: organochlorines, organophosphates, carbamates and pyrethroids (13). Organochlorine pesticides are lipophilic compounds with low vapor pressures and slow degradation rates (14). These are known for their toxicity, persistence in the environment, and bioaccumulation in the food chain. This last property was one of the main reasons why these were replaced by organophosphates pesticides, as they could be more easily degraded in the environment (15). Organochlorine insecticides were widely used between 1940s and mid 1960s, when they were discontinued due to their environmental effects (14). Organophosphates (OPs) are pesticides of low persistence in the environment, which are hydrolysed to high or low pH (16). These were developed during World War II as nerve gases, and their insecticidal properties were discovered shortly thereafter (17). The OPs have become widely used as replacements for organochlorine insecticides because they do not bioaccumulate in organism tissues or the environment (14). Carbamates are derivatives of the carbamic acid. These chemicals share the same mode of action with OPs, inhibiting the activity of acetylcholinesterase, although this effect can be more easily reversed, and the insects may recover at low doses (18). These last two types of insecticides have a broad spectrum of activity, rapid environmental degradation (19), relatively short biological half-lives, and are rapidly metabolized and excreted (14). The fourth group comprises pyrethroids, the most recently introduced insecticides (20), entering the marketplace in 1980 (21). They are considered safe due to their high insecticidal properties at low application rates, short persistence in the environment, no bioaccumulation and low mammalian toxicity (22), reasons supporting their extensive use (23).

Although there is abundant information regarding the chronological development of insecticides by chemical group, as shown in Table 1, in most cases, the records of the introduction and date of their use are not accurate. In general, each country has employed these chemicals based on its particular needs, in special, according to the occurrence or re-emergence of dengue outbreaks in a given time. The replacement of each pesticide for a new one depends on the resistance developed by the vector, and the criteria for effective insecticides considered relevant by authorities in each territory. Malathion, for example, has been one of the most frequently used. In Colombia, it has been utilized since 1980, and it is widely employed today (24). Mexico, however, suspended its use in 1999 (25). In Thailand, it was applied since 1950 but its arrest is not documented (26), and in Cuba it was abandoned with the introduction of pyrethroids (27). It is important to highlight that in some cases, pesticide use has been carried out combining different classes of insecticides, such as DDT with pyrethroids, although cross-resistance has been observed (28).

Table 1. History of the use of insecticides to control *Aedes aegypti*

Chemical group	Insecticide	Dosification (g/ha)		Introduction (year)	Used until	Replaced by	References
		Thermal fog	Cold spray				
Organochlorine	Dichloro-Diphenyl-Trichloro-ethane (DDT)	10 000-20 000 **		1940s	Mid - 1960s	Organophosphate and carbamates	14, 62
Organophosphate	Temephos	1 mg/L*		1950	Currently in use		10, 32
	Malathion	500 –600	112 – 600	Not reported	Some are currently used in certain parts of the world	Pyrethroids	13
	Methyl-pyrimifos	180 – 200	230 - 330				
	Fenitrothion	250 – 300	250 – 300				
	Chlorpyrifos	150 – 200	10 - 40				
Carbamates	Propoxur	-	100	1960s	Some are used Currently in certain parts of the world	Pyrethroids	63
	Bendiocarb	-	4 - 16				
Pyrethroids	Deltamethrin	0.5 – 1.0	0.5 – 1.0	1980	Currently in use		21
	Lambdacyhalothrin	1.0	1.0				
	Cypermethrin	-	1 – 3				
	Cyfluthrin	1 – 2	1 – 2				
	Permethrin	10	5				

* In water containers
** Active ingredient

Reports of chemical insecticide use to control dengue virus vectors

During the last decades, the use of chemical insecticides has been an important component to control the populations of dengue vectors (9, 29). Commercially available insecticides used in different countries are shown in Table 2. All these chemicals are not used simultaneously, but each country has employed specific insecticides throughout history, with peculiarities in both use and dosage form. A total of 40 countries from different continents recorded the use of insecticides for control of dengue during 2003-2005. The most widely used insecticides for vector control have been organophosphates and pyrethroids. In fact, a total of 262 tons of organophosphate (OP) insecticides and 39 tons of pyrethroids per year have been utilized (30).

Among OPs, in a global context, 76 % were utilized for space spraying, 23 % for larviciding, and 1 % for peri-focal spraying, interestingly, 90 % of the total was used in countries from the Americas. In the case of pyrethroids, 78 % was for space spraying, and the remaining percentage for peri-focal spraying. Pyrethroids were used for peri-focal spraying mainly in the Americas, and a very small quantity in the Western Pacific. About 50% of the total global usage of pyrethroid insecticides took place in countries from the Western Pacific and about 47 % in the Americas. The amount of OPs and pyrethroids used for dengue vector control constituted 60 % and 24 %, respectively, of the total annual use of insecticides (30).

Worldwide, the control of *A. aegypti* is mostly performed with OPs; being malathion the most frequently utilized, constituting 67 % of the average annual use, followed by temephos (22 %) (30). This last has been the leading pesticide used as larvicide in Malaysia (31), Port Suan City (Red Sea State) (32), Thailand (33), Panama, El Salvador, Cuba, Martinique Island, French Guiana, Peru, Brazil, Argentina, Venezuela and Colombia (22, 24, 27, 34-41).

Table 2. Insecticides used in different countries for the chemical control of *Aedes aegypti*

World Region	Country	Insecticide Used	References
Western Pacific Region	In general	Malathion, pyrethroids	33
South-East Asia	Thailand	Temephos, fenitrothion, malathion and propoxur, DDT Pyrethroids: permethrin, deltamethrin, cypermethrin	32, 26
	Vietnam	Organophosphates, pyrethroids	64
	Malaysia	Temephos, pyrethroids	30, 65
Africa	Port Suan City (Red Sea State)	DDT, fenthion, malathion, temephos, permethrin, deltamethrin, lambda - cyhalothrin	31
Américas	El Salvador	Deltamethrin, permethrin	35
	Cuba	Fenition, malathion, pyrethroids	27
	Mexico	DDT, malathion, permethrin based insecticides	25
	Panama	Temephos, malathion, fenthion and pyrethroids	34
	Brazil	Organophospates, mala thion, fenithrothion	66, 38
	Argentina	Temephos, Cis - permethrin	67, 39
	Colombia	Malathion, fenitrothion, deltamethrin, cyhalothrin, cyfluthrin	24
	Venezuela	Temephos, malathion	48
	French Guyana	Malathion, deltamethrin, fenitrothion, temephos	36
	Island Martinique (French West Indies)	Malathion, fenitrothion, deltamethrin	22
West Indies	Trinidad and Tobago	DDT, organophosphates	68

The main dengue vector control with pyrethroids has been performed with cypermethrin (37 %) and permethrin (45 %), followed by alpha-cypermethrin (14 %) (30). Other insecticides have also been critical for the control of *A. aegypti*, including fenthion, fenitrothion, chlorpyrifos, deltamethrin, cyhalothrin, cyfluthrin, propoxur, bendiocarb, dichlorodiphenyltrichloroethane (DDT) and dieldrin (22, 24, 27, 34-41).

According to WHO, during 2001, in terms of coverage, budget, human resources and amount of insecticide used, Brazil was the country with the most extensive program of control of *A. aegypti*. Reports from 2002 showed that in the Americas, vector control was mainly carried out with insecticides (42). In Colombia, for example, the main strategies conducted by local governments for vector control are aerial spraying of the insecticide, using thermal fogging or ultra-low-volume spraying, in particular with organophosphates, such as malathion (96 %), fenitrothion (40 %), or the pyrethroid compound, deltamethrin. Currently, insecticide spraying in Colombia is recommended for outbreaks, or when cases of Dengue Haemorrhagic Fever are confirmed (24).

Resistance registered in *Aedes aegypti*

The continued use of insecticides has induced pressure on populations of *A. aegypti*, leading to widespread resistance (43). Two main mechanisms have been reported to be responsible (28): the first involves an increased activity of detoxifying enzymes, including esterases, mixed function oxidases (cytochrome P450s), and glutathione S-transferases (GSTs) (44); and the second deals with structural changes in the insecticide target site in the central nervous system (45). The main insecticide targets are acetylcholinesterase, γ -aminobutyric acid (GABA) receptor and the voltage-gated sodium channel (46). In Latin America and the Caribbean, several *A. aegypti* populations have shown strong resistance to OPs, carbamates, and pyrethroids, existing correlations with elevated activities of at least one detoxification enzyme family. The resistance to OPs and carbamates is connected with acetylcholinesterase insensitivity (13, 46). In the case of temephos, for example, the resistance detected to this insecticide was related to the increased activity of esterases, specifically esterase A4 (9). In addition, several non-synonymous mutations in the gene encoding the trans-membrane voltage-gated sodium channel (kdr mutations) have been described to confer resistance to pyrethroids and DDT (22).

In countries such as Puerto Rico, Dominican Republic, Cuba, French Guiana, and Colombia, among others, have been recorded the resistance development of *Aedes aegypti* to insecticides such as temephos (9, 37, 38, 47-50) and pyrethroids (13, 37, 44, 51-54), showing with these, the evolution of resistance registered worldwide .

Because resistance records, as well as the registered effects in the health of humans, such as immunosuppression, endocrine disruption, reproductive abnormalities, irritant respiratory symptons, adverse genotoxic and neurological effects, and cancer (55-60), control of *Aedes* populations is being conducted through more environmentally friendly alternatives, such the use of plant extracts, reducing adverse effects on non-target organisms (61).

CONCLUSIONS

The vector control for *A. aegypti* has been one of the main strategies against dengue virus transmission, but it is mostly based on chemical insecticides, which induce resistance in mosquitoes and also cause damage to humans and the environment. This resistance is probably due to the lack of regulation in use and in the dosage of each case. This review supports the need to generate mosquito control strategies that are environmentally friendly with minimal affectations on human populations.

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