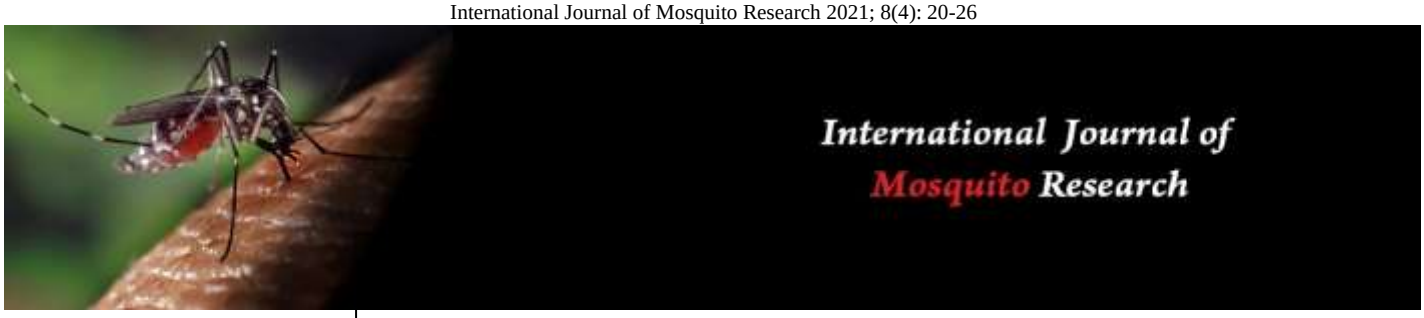

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Insecticide resistance status of *Aedes* mosquito vector in India: A review

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Abstract
In India, *Aedes* mosquitoes are well prevalent and play a key role in the transmission of vector borne diseases. Vector management is principally carried out by using various chemical insecticides since long, but consistent use has led to developing insecticide resistance which restricts the effectiveness of the control strategy. This review highlights the pieces of evidence on developing resistance level to major classes of chemical insecticides such as carbamates, organochlorines, organophosphates and pyrethroids with mechanisms of developed resistance in various regions of India. Insecticide resistant mechanisms which altered susceptibilities to insecticides can be categorized into two major groups as target site sensitivity and metabolic detoxification. Among different provinces of India, maximum level of resistance was observed against organochlorines (72%) followed by organophosphates (28%), pyrethroids (28%) and carbamates (16%). A summarized data on insecticide resistance status from all over India will be helpful to improve resistance management and epidemic disease control.

Keywords: *Aedes* mosquitoes, chemical insecticides, insecticide resistance, India, metabolic resistance, target site

Introduction
Aedes mosquitoes play a key role in the transmission of dengue, chikungunya, yellow fever and zika viruses. They are peri-domestic, anthropophilic, daytime biter, well flourishes in urban and suburban locations [1]. *Ae. aegypti* had its root in Africa [2], but later have spread in Southern North America, South and Central America, Southeast Asia, Middle East, Pacific and Indian Islands, Northern Australia and sporadically in the Europe [1]. They prefer mostly tropical, subtropical and temperate regions worldwide [3]. They laid eggs on a damp surface like tree holes and stagnant water in household containers like tires, vases, cans, animal watering dishes, water storage drums and naturally available holes in vegetation. *Aedes* breeding is high in monsoon and post-monsoon period which is directly associated with increasing cases of dengue [3, 4].

An estimated 50 to 100 million dengue virus infections are reported worldwide each year [1]. India has the highest number of dengue cases due to a growth in the size of the human population (15% of the world population) [5]. More than one lakh dengue infections cases have occurred annually in India over the past few years, resulting in high mortality and morbidity rates [6]. There is no vaccine, drug, antiviral therapy available against dengue and chikungunya, so prevention of these diseases primarily relies on the control of the mosquitoes vector population by using chemical insecticides.

Mosquitoes vector control is achieved primarily by removal of breeding sites and implementation of chemical insecticides, due to their fast action and significant efficacy. A variety of applications in the form of mosquitoes insecticide residual spray (IRS), space spraying, impregnated materials are often used for suppressing mosquitoes population [7]. Common classes of insecticides used for vector control are pyrethroids, organophosphates (OPs), organochlorines and carbamates. Unfortunately, worldwide extensive direct or indirect exposure to insecticides over a long period resulted in developing strategies to combat the targeted insecticide actions in mosquito's bodies known as resistance [6]. *Ae. aegypti* has developed tolerance to all insecticides classes- carbamates, pyrethroids, organochlorines, organophosphates worldwide [7]. Currently, pyrethroid insecticides are the most widely used insecticides for controlling mosquitoes worldwide [8].

Many modifications enable a mosquito to withstand deadly doses of insecticide. They can be conveniently divided into two major groups-target site insensitivity and metabolic detoxification. Sometimes by decreasing cuticular penetration by increasing sequestration insects helped them to develop resistance [9]. Therefore, monitoring of resistance level is a prerequisite to prevent resistance development in mosquitoes.
This review is therefore carried out to evaluate the associated current situation to provide data sets that will be required in improving public health of the human population in vector control management. This study aims to update and summarize recent evidence on resistance in *Aedes* species to stimulate further research to analyze the resistance level. It will help to critically review the current status of the problem and in managing *Aedes* population through the implementation of insecticide resistance management strategies more effectively.

History of insecticides in India

In India, the history of vector control is narrowly split into two pre-and post-DDT eras. During the pre dichlorodiphenyltrichloroethane (DDT) period (1902-1945) mosquito management was predominantly restricted to the use of larvivorous fishes, oils and Paris green in breeding sites and augmented by legislative techniques (measures). In 1944, DDT was implemented as a residual insecticide in the mosquito control program. Subsequently, trials of DDT in civilian areas of Odisha and Karnataka and then in Bombay were performed. Later, DDT was applied in the north-west and central India. Post DDT period started with the use of organochlorine insecticides BHC/HCH (Benzene hexachloride/hexachlorocyclohexane) in Assam in 1950. The management technique, however, was modified in 1953 (launched as National Malaria Control Programme) with the introduction of DDT, from larval control to adult mosquito control, focused on indoor residual spraying with insecticide to control malaria vectors. Later in 1969, malathion an organophosphate was introduced in Gujarat and Maharashtra as new chemicals to control DDT and HCH resistant mosquito vector population, but the species was confirmed to be malathion-resistant within four years, i.e. by 1973. Further, the Public Health Programme, launched new insecticides, synthetic pyrethroids in 1980. In the Ghaziabad district of Uttar Pradesh, the first trial of deltamethrin spray was performed and identified as a successful vector control measure. Lambda-cyhalothrin and cyfluthrin were implemented as an indoor residual insecticide during the last decade of the 20th century. Since the 1980s under the Public Health Programme temephos have been used to control the larval form of *Aedes* mosquitoes. Interventions in chemical regulation by the use of insecticides are becoming more and more frequent. Such insecticide-based interventions involve: aerosol, mosquito coil, mat and vaporized liquid for the residual purpose. Materials impregnated with insecticides such as nets and curtains are also abundant, utilizing the pyrethroid class in particular. Also, thermal spraying, surface residual spray, Ultra Low Volume (ULV) spraying was used to spread insecticides to eliminate adult mosquitoes [10].

Insecticide resistance and its causes

The widespread use of chemical insecticides has led to the development of insecticide resistance in mosquito vectors and is one of the factors reducing the success of vector control programmes [11]. The ability of an insect to tolerate those concentrations or doses of insecticides that would be lethal to a normal population is known as resistance. It is due to positive selection pressure, which exerts by an insecticide on low-frequency genes that are initially present in the vector [12]. Insecticide resistance production is a complicated phenomenon, relying specifically on physiological, genetic, behavioral and ecological influences and partially on the quantity and duration of insecticide application [9]. Six classes of insecticides are used for control of the vector population and every insecticide activates the selection of one or more resistance mechanisms with an enormous number of adult behavior changes [12, 13].

Resistance mechanisms divided into two groups

Minor group: It includes reducing penetration and behavioral resistance mechanisms.

Major group: It including metabolic resistance and target site resistance.

Behavioral resistance: Resistant insects can sense or identify a threat and escape the poison by moving from their usual behavior means as mitigating interaction with insecticides and hence reducing the ingestion. They can avoid eating if they come across such insecticides or quit the spraying area [9].

Cuticular resistance (Reduced penetration): Cuticular resistance is facilitated by thickening or altering the chemical properties of insect cuticle to reduce insecticide penetration into the insect body and it provides more time to metabolic enzymes for showing detoxification action [9].

Metabolic resistance: Metabolic detoxification is an acquired method of resistance, developed by improvement in insecticide detoxification [12]. Insecticide detoxification in mosquitoes includes three significant metabolic detoxifying gene families, namely-monooxygenases, esterase and glutathione-s-transferases. These genes usually enhanced metabolism through gene multiplication, the mutation in the coding sequence, enhanced up-regulation, or by a combination of these mechanisms [9, 12].

Target site insensitivity: Target site mutations change their binding affinities to specific insecticides which depend on the insecticide's molecular structure. Three main types of this mechanism are-insensitive acetylcholinesterase, insensitive GABA receptors, insensitive sodium channel regulatory proteins [9].

Cross-resistance: An insect with resistance to one insecticide has the potential to tolerate other insecticides is known as cross-resistance. It can occur in two forms positive and negative. When resistance occurs against many insecticides due to the expression of a single resistance mechanism is called positive cross-resistance, meanwhile, when the susceptibility of an insect to the insecticide "A" is increased caused by the development of tolerance against insecticide "B" and vice versa is known as negative cross resistance [12].

Multiple resistance: Multiple resistance exists in species of insects that tolerate two or more types of insecticide classes along with various action mechanisms [12].

Insecticide resistance status in India

Insecticide resistance status among dengue vectors is well documented in different parts of India and varied levels of resistance against many insecticides have been observed. Azeez, 1967 recorded the first time DDT resistance in adult *Aedes aegypti* from Jharia, Bihar, India [14]. Various studies revealed developing insecticide resistance in *Aedes* mosquito vectors from different provinces of the country [15, 18]. Hence, an attempt has been made to summarize and indicate the insecticide resistance in *Aedes* vector in different regions of India in Table 1.

Table 1: Insecticide resistance status of Aedes mosquito vector across different parts of India

S.No.	Mosquito Sp.	Location	Insecticide class	Reference
1.	*Aedes albopictus*	Maharashtra	DDT (Organochlorine)	19
2.	*Aedes aegypti*	Panji, Goa	DDT (Organochlorine)	20
3.	*Aedes aegypti*	Mandya, Karnataka	DDT (Organochlorine)	21
4.	*Aedes aegypti*	Delhi	DDT and dieldrin (Organochlorine)	22
5.	*Aedes aegypti*, *Aedes vittatus* and *Aedes w-albus*	Desert districts (Bikaner, Jaisalmer and Jodhpur) and three non-desert districts (Alwar, Ajmer and Jaipur)in Rajasthan	DDT and dieldrin (Organochlorine)	23
6.	*Aedes aegypti* and *Aedes albopictus*	Thiruvanantha- puram and Cochin International Airports in southern India	DDT and dieldrin (Organochlorine)	24
7.	*Aedes aegypti*	Andhra Pradesh	DDT (Organochlorine) and malathion (Organophosphate)	25
8.	*Aedes aegypti*	Ranchi (Jharkhand)	DDT (Organochlorine)	26
9.	*Aedes aegypti* and *Aedes albopictus*	Koderma (Jharkhand)	DDT (Organochlorine)	27
10.	*Aedes aegypti*	Bengaluru (Karnataka)	Propoxur (Carbamate)	28
11.	*Aedes aegypti*	Mumbai Port	Temephos, Fenthion (Organophosphate)	29
12.	*Aedes aegypti*	Delhi	Temephos (Organophosphate)-Possible resistance development	30
13.	*Stegomyia albopicta*	Assam	DDT (Organochlorine)	31
14.	*Aedes albopictus*	Kerala, Delhi, Gurgaon, Haridwar, Guwahati	DDT (Organochlorine) Deltamethrin, Permethrin (Pyrethroids)- incipient resistance	32
15.	*Aedes aegypti and Aedes albopictus*	Andaman and Nicobar	DDT (Organochlorine), Bendiocarb (Carbamate), Permethrin, Cyfluthrin Lambda-cyhalothrin (Pyrethroids), Fenitrothion (Organophosphate)	33
16.	*Stegomyia aegypti and Stegomyia albopicta*	Assam	DDT (Organochlorine), Temephos (Organophosphate)	34
17.	*Aedes aegypti*	Tamil Nadu	Permethrin (Pyrethroid)	35
18.	*Aedes aegypti*	Jaipur (Rajasthan)	Cypermethrin, Permethrin (Pyrethroids)- Possible resistance development	36
19.	*Aedes albpoictus*	Siliguri (West Bengal)	Temephos (Organophosphate)	37
20.	*Aedes albpoictus*	Northern West Bengal	DDT (Organochlorine) and Temephos (Organophosphate)	38
21.	*Aedes aegypti* and *Aedes albpoictus*	Assam and Arunachal Pradesh	DDT (Organochlorine)	39
22.	*Aedes aegypti*	West Bengal	Permethrin (Pyrethroid) and Propoxur (Carbamate)	6
23.	*Aedes aegypti*	NCR Delhi	DDT (Organochlorine)	40
24.	*Aedes albopicus*	West Bengal	DDT (Organochlorine), Permethrin (Pyrethroid) and Propoxur (Carbamate)	41
25.	*Aedes aegypti*	Bengaluru	DDT (Organochlorine), Deltamethrin and Permethrin (Pyrethroid)	42

Mechanisms of insecticide resistance

There are several resistance-inducing variables and the processes followed by species rely on the dominant pressure and the insecticide mode of action of the in use. A variety of major resistance mechanisms to different classes of insecticides have been detected in various parts of India. The development of resistance in *Aedes* species has led to multiple disadvantages in mosquito control programs. Increases in the rate of synthesis of detoxifying enzymes such as monooxygenases (MFOs), glutathione-S-transferases (GST) and carboxyl-cholinesterase (CCS) are due to the ability of mosquitoes to avoid the insecticidal action of these synthetic compounds. Non-specific esterase, glutathione S-transferase (GSTs) and P_{450} mediated monooxygenase (MFOs) are believed to be active in the detoxification of organophosphate, pyrethroid, and carbamate insecticides within the metabolic-based insecticide resistance system. MFOs are frequently accompanied by pyrethroid metabolic resistance, although GSTs are typically involved with resistance to organochlorides. The magnification of CCE activity results in resistance to pyrethroids, organophosphates and carbamates. In one of the three target sites, namely the voltage-gated sodium channel genes, acetylcholinesterase and gamma-aminobutyric acid (GABA), target-site insensitivity arises from point mutations. Resistance to organochlorines and pyrethroids is regulated by the voltage-gated sodium channel insensitivity system, also referred to as Kdr. Resistance to organophosphates and carbamates is regulated by the acetylcholinesterase insensitivity process, while resistance to cyclodiene insecticide is largely responsible for the GABA-insensitivity mechanism. In pyrethroid resistance, multiple point mutations in the para gene of *Aedes aegypti* have been identified. The mutants G119S, S989P, V1016G, T1520I, F1534C, and F1534L are precisely reported to generate the kdr phenotype. In acetamiprid and deltamethrin selected strains, a slightly thicker cuticle was seen compared to the parental strain, which likely prevented the penetration of insecticides into selected larvae, resulting in the development of resistance [43]. Resistance mechanism reported from different areas of India is depicting in Table 2.

Table 2: Resistance mechanism in Aedes vector across different locations of India

S.No.	Mosquitoes sp.	Location	Resistance mechanism	Insecticide class	References
1.	*Aedes aegypti*	Maharashtra	Glutathione S-transferase (Metabolic resistance)	Organochlorine	44
2.	*Aedes aegypti*	Tamil Nadu	Acetylcholin esterase (Target site insensitivity) and Glutathione S-transferases (Metabolic resistance)	Organophosphate and Pyrethroids	45
3.	*Aedes albopictus*	Assam	Esterases and Glutathione S-transferases (Metabolic resistance)	Organochlorine	46
4.	*Aedes aegypti*	Tamil Nadu	Esterases and mixed-function oxidase (Ace 1- G119S mutation) (Metabolic resistance)	Organophosphate	47
5.	*Aedes aegypti*	Tamil Nadu	Glutathione S-transferases and carboxylesterase (Metabolic resistance), Kdr mutation- F1534C (Target site insensitivity)	Pyrethroids	35
6.	*Aedes aegypti*	Delhi	Kdr mutation (F1534C & T1520I) (Target site insensitivity)	Organochlorine and Pyrethroids	48
7.	*Aedes albopictus*	West Bengal	Esterases (Metabolic resistance)	Organophosphate	37
8.	*Aedes aegypti*	West Bengal	Carboxylesterase (Metabolic resistance)	Organophosphate	6
9.	*Aedes albopictus*	Odisha	Esterases and Cytochrome P_{450}s (Metabolic resistance)	Pyrethroids and Organophosphate	49
10.	*Aedes aegypti*	Jaipur	Glutathione S-transferases and alpha esterase (Metabolic resistance)	Pyrethroids	50, 51
11.	*Aedes aegypti*	West Bengal	Alpha esterase and Beta esterase (Metabolic resistance)	Organophosphate and Carbamate	52
12.	*Aedes aegypti*	West Bengal	Metabolic resistance	Pyrethroids and Carbamate	53
13.	*Aedes aegypti*	West Bengal	Kdr or VGSC gene mutation (V1016G + F1534C) (Target site insensitivity)	Organochlorine	54
14.	*Aedes aegypti*	Bengaluru	Kdr mutation (F1534L, F1534C, S989P, V1016G) (Target site insensitivity)	DDT and Pyrethroids	55
15.	*Aedes aegypti*	Bengaluru	F1534L, S989P, F1543C, V1016G- Kdr mutation (Target site insensitivity)	Pyrethroids	42

Discussion

In India, mosquito control initiatives toward *Aedes* mosquitoes are mainly focused on the use of temephos, insect growth regulators (diflubenzuron, pyriproxyfen) as a larvicide, thermal fogging and malathion ultra-low-volume space spray to regulate dengue outbreaks and to minimize human vector interaction by using pyrethroid-treated bed nets. DDT has been utilized as an indoor residual spray (IRS) until recently and has been supplemented by a synthetic pyrethroid [56]. The extensive use of chemical insecticides for a long time has contributed to the emergence of resistance to insecticides in vector mosquitoes. Insecticide resistance processes in mosquito vectors are being researched worldwide as they elaborate the routes of production of resistance and assist in emerging methods to avoid and delay exposure to insecticides. Most of the research analyzed has shown that the adult mosquitoes of *Aedes aegypti* and *Aedes albopictus* are resistant to DDT, but remain vulnerable to malathion, temephos, propoxur, and fenitrothion in general. It was also observed that the larval phases of *Aedes aegypti* and *Aedes albopictus* were immune to DDT but susceptible to larvicides, namely temephos, fenthion and malathion. Diverse level of cross-resistance to malathion, fenthion, DDT and Chlorpyrifos also observed in *Aedes* species.

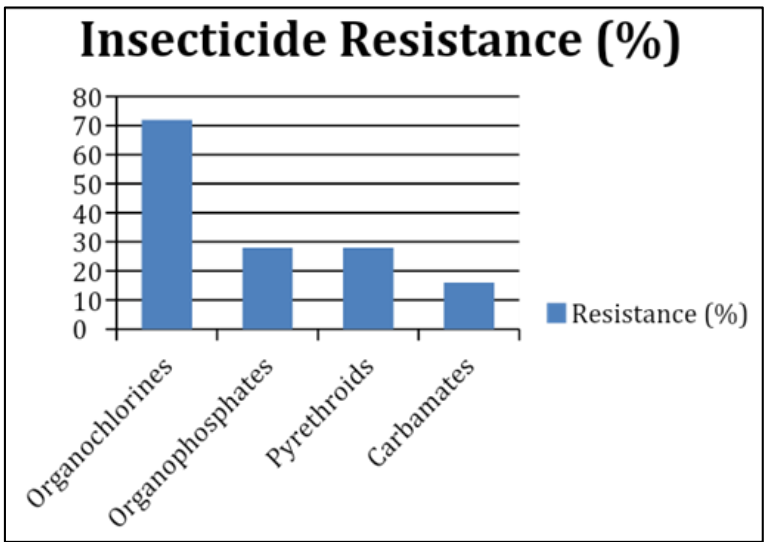

Fig 1: Insecticide resistance percentage in Aedes vectors in India

According to the data on resistance in Table -1 the resistance percentage towards different classes of insecticides is observed as follows- 72% against organochlorines, 28% against organophosphates, 28% against pyrethroids, 16% against carbamates, respectively (Fig 1).

This may indicate the likelihood of this resistance phenomenon becoming prevalent in the immediate future. The study will help to generate basic information on the current resistance status in *Aedes* vectors to address the knowledge gaps between dengue species distribution and insecticide resistance incidences.

Conclusion

Knowledge of emerging resistance in dengue vectors will give the chance to improve the policy more effectively to mitigate resistance arising from local applications of insecticides used in dengue control operations. Furthermore, it is recommended to analyze the exact contribution factors in the current

distribution of insecticide resistance in dengue vectors. Hence the imperative for control programs to mount management strategies to curb the spread of resistant population, as identified by a variety of research activities in many areas of India. The uses of a multidisciplinary approach to mosquito control (non-insecticidal methods) such as repellent trees, most of which are native, are possible replacements to synthetic insecticides.

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