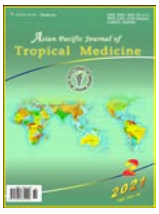

Review Article

Asian Pacific Journal of Tropical Medicine

apjtm.org

doi: 10.4103/1995-7645.306737

Impact Factor: 1.94

Insecticide resistance status and biochemical mechanisms involved in *Aedes* mosquitoes: A scoping review

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ABSTRACT

Mosquitoes belonging to the genus *Aedes* pose a significant threat to human health on a global scenario due to their role in transmission of dengue, chikungunya, zika, and yellow fever. In absence of specific medications and vaccines against these diseases, disease prevention relies on vector control. However, in today's world, vector control is facing major challenges due to the onset of insecticide resistance in mosquitoes. There are four main mechanisms of insecticide resistance, namely, behavioral resistance, reduced penetration/cuticular resistance, metabolic detoxification, and target site resistance; however, the latter two mechanisms have been studied widely in *Aedes* mosquitoes. Insecticide resistance in *Aedes* mosquitoes is widespread throughout the world. This review compiles the degree of insecticide resistance/susceptibility prevailing among different field populations of *Aedes* mosquitoes worldwide. In addition, the review has detailed the mechanisms providing the resistance phenomenon observed in nature in *Aedes* mosquitoes.

KEYWORDS: *Aedes aegypti*; *Aedes albopictus*; Insecticide resistance; Metabolic detoxification; Knockdown resistance

1. Introduction

Mosquitoes threaten human health due to its key role in transmission of diseases such as malaria, dengue, chikungunya, Japanese encephalitis, filariasis, *etc*. Dengue and yellow fever collectively infect 50-100 million people every year, with over 2.5 billion people living in disease-endemic areas[1]. *Aedes* mosquitoes, namely, *Aedes (Ae.) aegypti* and *Ae. albopictus* are responsible for the transmission of dengue virus (DENV) and chikungunya virus[2]. As an impact of increased trade and transport, both the mosquito species have geographically extended their distribution to many previously unexplored areas[3]. Dengue poses a major challenge to India because of the presence of all four dengue virus serotypes along with a novel serotype[4,5].

In India, more than 100 000 cases of dengue occurred in 2016 and till November 2017, the previous year data has already been surpassed with 1 29 329 cases of infections and 200 deaths[6]. During the last few decades, this disease has emerged as one of the fastest spreading vector-borne diseases in India. The high human population density, large vegetation cover, and ideal abiotic factors for mosquito growth increase the risk of mosquito-borne infections, *i.e.* DENV, chikungunya virus, *etc* in India[7]. The spatial distribution of both *Aedes* species overlaps with each other, however *Ae. aegypti* is said to prefer urban areas, whereas *Ae. albopictus* prefers rural areas, *i.e.* areas with more vegetation[8].

Since the discovery of insecticides, they have been used heavily for mosquito control. As no drug or vaccine is available for the treatment of dengue/dengue haemorrhagic fever, the only method for preventing the disease spread is through the control of vector mosquitoes *i.e. Aedes* mosquitoes[9,10]. In India, many measures are adopted for mosquito control, *e.g.*, biological control, chemical control, environment management, and source reduction methods, personal prophylactic measures, *etc*[6]. Insecticide treatment of bednet, curtains, windows, water storage cans, *etc*. have been reported to be highly effective at minimising the household *Aedes* mosquito infestation[11]. For chemical control of mosquito larvae, larvicides such as temephos or insect growth regulators (pyriproxyfen, diflubenzuron) are used[6]. For adult mosquito control, indoor residual spray (with 2% pyrethrum extract), outdoor space spraying [ultra low volume (ULV) malathion spray], thermal fogging (malathion/pyrethroid) are applied[6].

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How to cite this article: Bharati M, Saha D. Insecticide resistance status and biochemical mechanisms involved in *Aedes* mosquitoes: A scoping review. Asian Pac J Trop Med 2021; 14(2): 52-63.

Article history: Received 30 April 2019 Revision 4 August 2020
Accepted 10 August 2020 Available online 20 January 2021

In India, organochlorines (OCs) *e.g.* dichloro-diphenyl-trichloroethane (DDT), dieldrin, aldrin; organophosphates (OPs) *e.g.* malathion, temephos, dichlorvos, chlorpyrifos; synthetic pyrethroids (SPs) *e.g.* lambda-cyhalothrin, deltamethrin, permethrin, cypermethrin, and its derivatives-cyfluthrin; and carbamates (CBs) *e.g.* propoxur, bendiocarb have been widely used for both mosquito control as well as agricultural pest control[7]. Similarly, ULV spray and thermal fogging have also been shown to be effective in reducing the risk of dengue virus transmission throughout the world[12].

Owing to the heavy use of these chemicals/insecticides, both target as well as non-target species have evolved to resist the actions of those chemicals in their body through different mechanisms which is known as insecticide resistance[13]. Insecticide resistance results in the failure of mosquito control programmes to achieve their targets, thus increasing the risk of DENV infection[13].

Resistance to insecticides can be caused by an array of modifications within a mosquito, namely, behavioural alteration, physiological modifications within the cuticle reducing the insecticide penetration, biochemical changes within the activity of major insecticide detoxifying enzymes, or structural modification within the insecticide target thereby blocking the insecticide binding/action[14]. Varying degrees of insecticide resistance has been reported in both *Ae. aegypti* and *Ae. albopictus* worldwide.

Mosquitoes have developed insecticide resistance both as a direct effect of insecticides targeted on them as well as an indirect exposure of insecticide sprayed on agricultural field[7,15–17]. Also, the household prophylactic measures *i.e.* use of mosquito repellent coils, creams, lotions, fumigants contain formulations of synthetic pyrethroids (recent compounds contain trans allethrin) also resulted in insecticide resistance development[18].

Overexpression of insecticide detoxifying enzyme classes, such as carboxylesterases (CCEs), glutathione-S-transferases (GSTs), and cytochrome P450s (CYP450) or mixed-function oxidases (MFOs) have been reported to confer insecticide resistance in many populations of insecticide-resistant *Ae. aegypti* and *Ae. albopictus* population worldwide[1,19]. Numerous point mutations conferring target site alteration in voltage-gated sodium channel gene and acetylcholinesterase (AchE) gene have also been identified in *Ae. aegypti* mosquitoes[1,19]. Presence of knockdown resistance (kdr) mutations such as, F1534C, V1016I, V1016G, *etc*. has been shown to provide varying degrees of selective advantage under insecticide pressure in many populations of *Ae. aegypti*[11,20,21].

Knowledge of the distribution and abundance of dengue virus-carrying *Aedes* mosquitoes is essential for the accurate prediction of dengue outbreak season and thereby proper planning for mosquito control before the disease appearance. However, disease prevention is highly dependent on effective vector control alone[22]. So, the information regarding the prevailing status of insecticide resistance and the underlying mechanism of resistance in the field/wild populations of *Aedes* mosquitoes may help in the efficient planning of mosquito control strategy. The present study summarized the prevailing degree of insecticide resistance along with the involved mechanism in action throughout different corners of the world. The overall trend presented here may help devise approaches to delay or control the onset of insecticide resistance in *Aedes* mosquitoes.

2. Methodology for reviewing insecticide resistance in *Aedes* mosquitoes

The data interpreted for this study involve the result of WHO susceptibility assays using standard insecticide dosages for larva[23] and exposure to insecticide-impregnated paper for adults[24]. Research articles, where other parameters were studied for the study of insecticide resistance, were not included for the analysis because data from the study of different parameters are not comparable and such comparison may lead to erroneous interpretations. Earlier literature on the same topic has already been reviewed[1,19]. So, the present study is a compilation of scientific studies conducted from 2012 till 1 March 2018. Papers with studies on insecticide resistance/susceptibility in *Aedes* mosquitoes (keywords: *Aedes* insecticide susceptibility/resistance; *Aedes* susceptibility/resistance status; Mosquito insecticide susceptibility/resistance; *Stegomyia* insecticide susceptibility/resistance; dengue vector insecticide resistance) were obtained from Google Scholar and Pubmed. Altogether 104 papers were retrieved related to the topic studied and 84 papers with insecticide susceptibility testing performed following WHO bioassay were selected and analysed for the preparation of this article (Figure 1).

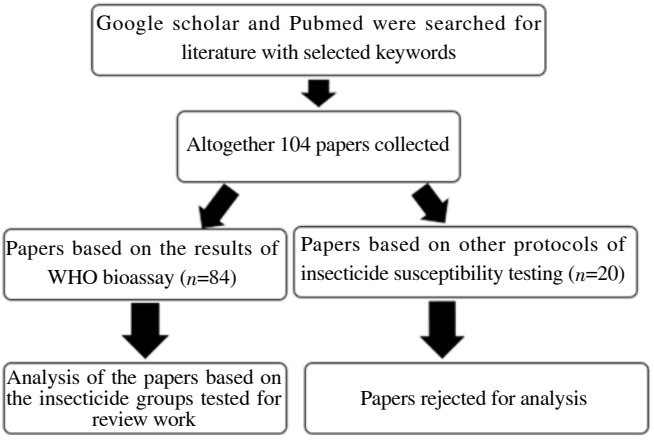

Figure 1. Flowchart of literature selection for analysis and review.

3. Insecticide resistance in *Aedes* mosquitoes

From the studies conducted throughout the world, widespread resistance against different insecticides has been observed in *Aedes* mosquitoes. The status of insecticide resistance in *Ae. aegypti* is provided in Table 1 and that of *Ae. albopictus* in Table 2. The following section will be focusing on the insecticide resistance/susceptibility in *Ae. aegypti* followed by *Ae. albopictus*.

3.1. Insecticide resistance in Ae. aegypti

Present status of insecticide resistance in *Ae. aegypti* has been summarized in Table 1. In many studies, both the resistance status and the mechanisms involved have been studied. Resistance against four groups of insecticides namely, OCs, OPs, SPs, and CBs have been studied in the majority of the conducted studies (Table 1 and Figure 2). The proportion of mosquitoes either susceptible or resistant/intermediate resistance to insecticides has been depicted in pie chart form (Figure 2) to provide an overall idea about the prevailing resistance status throughout the studies conducted over the world. Each pie represents the proportion of that particular insecticide contributing towards the resistance/incipient resistance or susceptibility amongst all the literature studied. From the pie chart (Figure 2A), it is very clear that amongst the studied literature, maximum cases of resistance in *Ae. aegypti* was noted against deltamethrin and temephos. Similarly, the maximum cases of incipient resistance (Figure 2B) were also noted against the same insecticides, *i.e.* deltamethrin and temephos. Whereas, the maximum cases of susceptibility in *Ae. aegypti* mosquitoes were noted against malathion (Figure 2C). However, in the majority of the studies, the mechanism conferring insecticide resistance was found to be either metabolic detoxification or target site alteration, or both.

3.1.1. Resistance against OCs

DDT resistant strains of *Ae. aegypti* have been reported from Sri Lanka, Mexico, Nigeria, Central Africa, Malaysia, Pakistan, Saudi Arabia, Colombia, India and Cameroon (Table 1). Highly resistant strains (with corrected mortality: 0%-2%) have been observed in Malaysia and Colombia. Rest of the reported strains showed low to moderate resistance against DDT. Moreover, only one DDT susceptible strain of *Ae. aegypti* was reported worldwide.

Resistance against DDT may be contributed either by increased activity of insecticide detoxifying enzymes or by target site mutations, *i.e.* kdr mutations or by a combination of both. In some studies, resistance to DDT was found to be a multifactorial phenomenon, *i.e.* both elevated CCEs and GSTs along with a prevalence of kdr mutations, namely V1016L (on IIS6 domain of sodium channel gene) and F1534C (on the same gene and domain), were shown to contribute to resistance phenomenon[20]. However, in other studies, either metabolic detoxification alone *i.e.* enhanced α- and β-CCEs, CYP450 MFOs, GSTs[26], or kdr mutation, *i.e.* I1016[35] was found to be the underlying mechanism. In another study of such types, kdr F1534C (frequency 0.41-0.79) was found to be associated with DDT resistance in *Ae. aegypti*[38]. Moreover, some other authors have pointed on sex-based/sex-limited resistance mechanisms. In one such study, differences were noted between male and female resistance mechanisms, *i.e.* in male *Ae. aegypti* mosquitoes, detoxification through CYP450s was found to confer the observed resistance against DDT whereas, in females, this enzyme group could not account for the total observed resistance[28]. Still, the exact mechanism or group of mechanisms conferring resistance against DDT remains unsolved.

3.1.2. Resistance against OPs

OPs used worldwide for insecticide resistance studies include temephos, chlorpyrifos, fenitrothion, dichlorvos, and malathion for larvae and only malathion for adults. Temephos has been the most commonly used mosquito larvicide throughout the world since the late 1960s[81]. Also, resistance to this larvicide has been observed throughout different strains of *Ae. aegypti* from different corners of the world (Table 1). Advanced studies have been made to identify the major underlying mechanism behind temephos resistance. The resistance to temephos has mostly been correlated with metabolic detoxification, either through biochemical CCE assay or more advanced tools like microarray or detox chip studies. Enhanced detoxification enzymes have been reported to provide resistance against temephos in advanced studies[44,82].

A clear correlation between α- and β-CCEs and GSTs and temephos resistance have been found in *Ae. aegypti* in Brazil with no role of altered AchEs behind resistance[44]. Some α- and β-CCEs and CYP450s have been found to provide resistance against temephos[48]. In most studies, resistance to temephos has been linked mainly to CCEs. Microarray studies have reported two CCE genes namely, *CCEae3A* and *CCEae6a* to be the main candidate genes behind resistance to temephos in *Ae. aegypti*[83]. Also, it was reported that the above-mentioned genes may have undergone gene duplication to provide resistance in *Ae. aegypti*[83]. However, the role of amino acid substitution in the gene could not be rejected. Similar observations were also made by other studies[21,39], in which both CYP450s and CCEs were shown to be upregulated in temephos resistant strains of *Ae. aegypti*. CYP6M11 has also been found to be highly overexpressed during temephos resistance[39,67]; other members of CYP450 family CYP6F3, CYP6N12, CYP9M9 were also found to be related to temephos resistance in *Ae. aegypti*[39,67].

In other studies, a somewhat different pattern of resistance mechanism was observed. Through synergistic studies, CCEs were reported to be the main enzyme group conferring resistance against temephos in *Ae. aegypti*; however, no upregulated *CCE* gene could be observed in the same strain[21,67]. Rather, CYP450s were reported to be upregulated in those temephos resistant strains of *Ae. aegypti*[21,67]. Such findings question the specificity of enzyme inhibitors and the sequence similarities of different detoxifying enzyme groups.

Many studies claim to confirm the role of CCEs in temephos resistant *Ae. aegypti* populations. In an Indian temephos resistant *Ae. aegypti* population, the observed resistance was conferred by both metabolic detoxification through α- and β-CCEs and target site

Table 1. Insecticide resistance status and biochemical mechanisms involved in *Aedes aegypti*.

Tested insecticide	Country	Mechanism of resistance
DDT	R (Sri Lanka[12], Mexico[20], Nigeria[25], Central Africa[26,27], Malaysia[28–30], Pakistan[31–33], Saudi Arabia[34], Colombia[35], India[36–38], Cameroon[39]) S (Nigeria[40]) IR (Nigeria[25], Ghana[41])	Elevated activity of detoxifying enzymes[20,26,28] Target site modified *via* kdr mutation[20,28,38]
Dieldrin	R (Malaysia[28]) S (Malaysia[28], India[36]) IR (Malaysia[30])	-
Temephos	R (French West Indies[21], Malaysia[28], Martinique island[42], Costa Rica[43], Brazil[44,45], Indonesia[46–49], Chile[50], Colombia[35,51,52], Latin America[53], India[37,54], Sri Lanka[55]) S (Central Africa[26], Colombia[35], India[36,54,56], Puerto Rico[57], Argentina[58], Thailand[59]) IR (Pakistan[33], Colombia[51], India[54], Brazil[60,61], Singapore[62])	Elevated activity of detoxifying enzymes[26,28,43,44,48] Target site modified *via* kdr mutation[51,61] Highly insensitive AchE[21]
Malathion	R (Sri Lanka[12], French West Indies[21], Malaysia[28], Pakistan[32,33], Indonesia[47,49], Yemen[63], Indonesia[64], Malaysia[65], U.S.A.[66] S (Sri Lanka[12], Malaysia[28,29], Pakistan[31], Colombia[35,52], India[37], Cameroon[39], Brazil[45], Indonesia[48], Chile[50], Haiti[67]) IR (Malaysia[30], India[36])	Metabolic detoxification through enzymes[12,28,48] Resistance against malathion related to CCEs[12] Highly insensitive target, AchE[21]
Fenitrothion	R (Saudi Arabia[34], India[36], Yemen[63]) S (Central Africa[26,27], Malaysia[29], Colombia[52], Argentina[58])	-
Chlorpyrifos	R (Mexico[68]) S (Costa Rica[43], Argentina[58])	-
Primiphos methyl	R (Colombia[35], Colombia[52]) S (Malaysia[22], Singapore[69])	-
Dichlorvos	R (India[70])	-
Lambdacyhalothrin	R (Malaysia[22], Central Africa[27], Pakistan[31], Pakistan[32], Saudi Arabia[34], Ghana[41], Yemen[63], Mexico[68], India[70], China[71]) S (Central Africa[27], Pakistan[32], Saudi Arabia[34], Ghana[41], Argentina[58], Cote d'Ivoire[72]) IR (Pakistan[31], India[36], China[71], Tanzania[73])	Metabolic detoxification through CCEs[52]
Deltamethrin	R (Mexico[11], Mexico[20], French West Indies[21], Central Africa[27], Malaysia[28], Malaysia[30], Pakistan[31,32], Saudi Arabia[34], Colombia[35], India[36,38], Martinique island[42], Costa Rica[43], Brazil[44], Chile[50], Latin America[53], Sri Lanka[55], Brazil[60], U.S.A.[66], Mexico[68], Singapore[69], Venezuela[74]) S (Nigeria[25], Central Africa[26,27], India[37], Colombia[52], Argentina[58], Yemen[63], Haiti[67], Cote d'Ivoire[72]) IR (Nigeria[25], Central Africa[26], Cameroon[39], Ghana[41], Sri Lanka[55], Thailand[59], Tanzania[73])	Elevated activity of metabolic enzymes[20,21,28,30,42,74] Target site resistance through prevalent kdr mutations[20,21,28,35,38]
Permethrin	R (Mexico[20], Malaysia[28–30], Pakistan[33], Saudi Arabia[34], Colombia[35], India[38], Brazil[45], Indonesia[48,75], Thailand[59], Singapore[62,69], Mexico[68]) S (Nigeria[25], Central Africa[27], Cameroon[39], Nigeria[40], Ghana[41], Argentina[58], Yemen[63], Haiti[67], Cote d'Ivoire[72]) IR (Pakistan[31], India[36], Thailand[59], Haiti[67], Tanzania[73])	Metabolic detoxification through enzymes[28,30,48] Target site resistance through prevalent kdr mutations[20,28,35]
Cyfluthrin	R (Colombia[35]) S (Saudi Arabia[34], Yemen[63]) IR (Malaysia[29], India[36])	Target site modification, kdr mutation might be linked[35]
Cypermethrin	S (Costa Rica[43], Argentina[58]) R (Brazil[45], Chile[50], Latin America[53], Mexico[68], China[71]) IR (China[71])	-
Etofenprox	R (Singapore[62,69])	-
Bifenthrin	R (Mexico[68])	-
Sumithrin	R (U.S.A.[66])	-
Propoxur	R (Sri Lanka[12], Central Africa[27], Malaysia[29], India[56], Cote d'Ivoire[72]) S (Sri Lanka[12], Central Africa[26,27], India[36]) IR (Cote d'Ivoire[72])	Elevated activity of detoxifying enzymes[26]
Bendiocarb	R (Malaysia[28–30], Pakistan[31,56], Saudi Arabia[34], India[36], Cameroon[39], Nigeria[40]) S (Mexico[11], Costa Rica[43]) IR (Mexico[11], Pakistan[32])	Metabolic detoxification through enzymes[28,30]
Diflubenzuron	S (Brazil[44], Chile[50])	-

Note: R: Resistant, IR: Incipiently resistant, S: Susceptible. Kdr mutation: Knockdown resistance mutation. AchE: Acetylcholinisterase. CCEs: Carboxylesterases. -: Mechanism not found/studied.

Table 2. Insecticide resistance status and biochemical mechanisms involved in *Aedes albopictus*.

Tested insecticide	Resistance status and region	Mechanism of resistance
DDT	R (Sri Lanka[12], Central Africa[26], Malaysia[30], Pakistan[31,33], India[36,37,76,77], U.S.A.[78], China[79]) S (Malaysia[28,30]) IR (Malaysia[30])	Enhanced activity of insecticide detoxifying enzymes, CYP450s[30], CCEs[76], GSTs[76,78])
Dieldrin	S (Malaysia[28,30], India[36]) R (Malaysia[30]) IR (Malaysia[30])	-
Temephos	R (Central Africa[26], India[36,37], Sri Lanka[55], China[79], Malaysia[80]) S (India[7], Central Africa[26], Malaysia[28], U.S.A.[78], India[77]) IR (India[7], Pakistan[33], Sri Lanka[55])	Elevated activity of insecticide detoxification enzymes, CCEs[7,26] and GSTs[26]
Malathion	R (Malaysia[30], Pakistan[33]) S (India[7], Malaysia[28,30], Pakistan[31], India[36,37,77], Haiti[67]) IR (Malaysia[30], India[37], U.S.A.[78])	Enhanced detoxification *via* β-CCEs[78]
Fenitrothion	R (Central Africa[26], India[36]) S (India[36])	-
Primiphos methyl	R (Malaysia[22])	-
Dichlorvos	S (China[79])	-
Lambdacyhalothrin	R (Malaysia[22], Pakistan[31]) S (India[7], Pakistan[33]) IR (Pakistan[31], India[36])	-
Deltamethrin	R (Central Africa[26], Malaysia[28], Pakistan[31], China[79]) S (India[7,36,37,76,77], Central Africa[26], Malaysia[28,30], Pakistan[33], Sri Lanka[55], U.S.A.[78], Haiti[67]) IR (Malaysia[30])	Elevated activity of metabolic enzymes[20,21,28,30,42,74] Target site resistance through prevalent kdr mutations[20,21,28,35,38]
Permethrin	R (Sri Lanka[12], Malaysia[28], Pakistan[31,33], India[36], China[79]) S (Malaysia[28,30], Haiti[67]) IR (Malaysia[30])	Target site modification *via* kdr based mechanism[12] Enhanced detoxification *via* CYP450s[28]
Cyfluthrin	IR (India[36])	-
Cypermethrin	R (China[79])	-
Pallethrin	S (U.S.A.[78])	-
Propoxur	R (Central Africa[26], U.S.A.[78], China[79]) S (Sri Lanka[12], Central Africa[26], India[36], U.S.A.[78])	Target site insensitivity through lower AchE activity[28]
Bendiocarb	R (Malaysia[30], Pakistan[31,33], India[36]) S (Malaysia[28,30]) IR (Malaysia[30], Pakistan[31])	Enhanced activity of detoxifying enzymes through CYP450s[30]
Methoprene	S (U.S.A.[78]) R (U.S.A.[78])	-
Pyriproxyfen	S (U.S.A.[78]) R (U.S.A.[78])	-

Note: R: Resistant, S: Susceptible, IR: Incipiently resistant. Kdr mutation: Knockdown resistance mutation. AchE: Acetylcholinesterase. CCEs: Carboxylesterases. GSTs: Glutathione S-transferase. CYP450s: Cytochrome P450s. -: Mechanism not found/studied.

mutation, G119S in *ace–1* gene[84]. A deeper insight revealed that all three major detoxifying enzyme groups get upregulated to provide resistance against temephos in *Ae. aegypti*, however, CCEs do have a predominant role[82].

Through an indirect study incorporating quantitative trait loci (QTL) mapping to identify the resistance genes, a single QTL, *rtt1* (resistance to temephos) was identified in chromosome 2 of *Ae. aegypti*[85]. This QTL was later identified as a cluster of CCE gene, supporting the strong correlation between CCEs and temephos resistance in *Ae. aegypti*[85].

Though target-site resistance has not been found to be linked to temephos resistance, yet a temephos resistance resistant strain of *Ae. aegypti* with a high prevalence of V1016I mutation was reported in Brazil[61]. In context to temephos resistance in *Ae. aegypti*, it may be noted that there are more pieces of evidence of metabolic detoxification playing the major role than target site alteration.

Many field strains of *Ae. aegypti* mosquito have been reported to exhibit varying patterns of resistance against other members of OPs. Some studies support the phenomenon of cross-resistance between temephos and malathion[48], however, some others strongly reject it[21]. *Ae. aegypti* strains have been found to be resistant to temephos yet susceptible to malathion, fenitrothion, or other OPs[21]. This may pertain to the fact that open-chain OPs may have different resistance mechanisms than other OPs[86]. Resistance against malathion may be conferred by some completely different mechanism than that against temephos[21]. However, as for temephos, resistance against malathion has also been correlated with enhanced activity levels of CCEs[64]. In other studies, no single enzyme, rather a mixture of different enzyme groups, *i.e.* both CCEs and CYP450s were reported to provide resistance against malathion[48]. Few studies strongly reject the involvement of GSTs in resistance against malathion[65], whereas some others support it. Through advanced studies, it was revealed

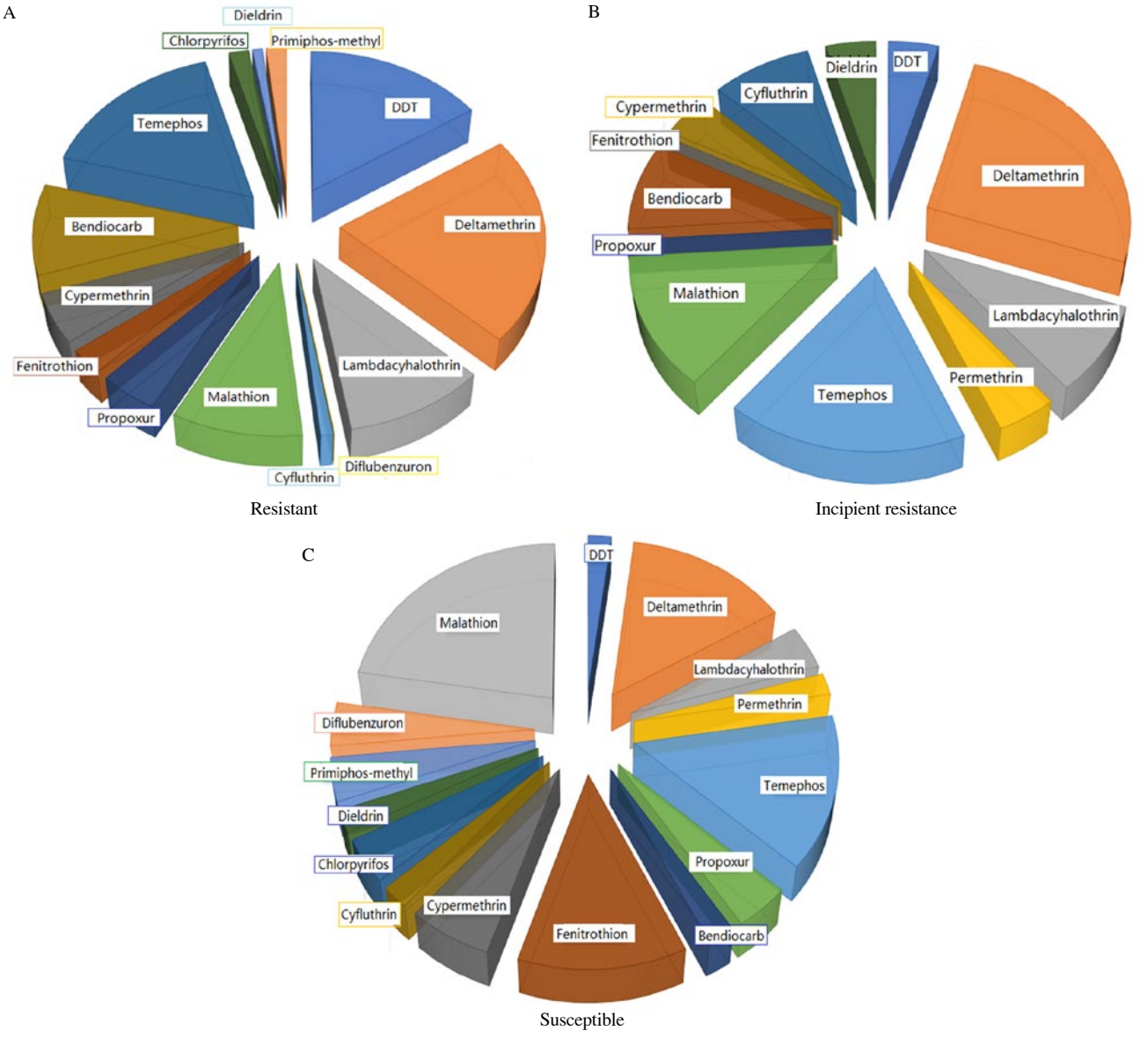

Figure 2. Depiction of insecticide susceptibility status against various insecticides in *Aedes aegypti* mosquitoes.

that CCEs and GSTs may play vital roles in conferring resistance against malathion[87]. Similarly, for resistance against other OPs, *i.e.* fenitrothion and dichlorvos, a mixture of different groups of detoxification enzymes was found to be responsible[70,88,85]. Enhanced activity levels of both CCEs and AchEs were shown to provide resistance against dichlorvos in an Indian strain of *Ae. aegypti*[70]. GSTs may also prove to be strong candidates for detoxification of OPs[87].

3.1.3. Resistance against SPs

SPs are the newest among the insecticide groups, however, most frequent resistance has been observed in both type Ⅰ and type Ⅱ pyrethroid insecticides (Table 1). Deltamethrin was the first pyrethroid insecticide to be introduced in mosquito control in the late 1980s. Subsequently, other pyrethroid compounds were discovered and brought into use. SP insecticides target the voltage-gated sodium channel to manifest their action, *i.e.* same as DDT[13]. Moreover, pyrethroid insecticide was reported to develop resistance at a very fast rate which may be due to cross-resistance, *i.e.* moderate to high resistance against DDT is already widespread in *Ae. aegypti* and both SPs and DDT share the same target site.

SP resistance is thought to be conferred mainly by metabolic detoxification and target-site mutation. Many previous reports have been made on the promising role of detoxifying enzymes, *i.e.* CYP450s (mainly), CCEs, and GSTs (lesser extent)[1]. However, since 2012, very few reports have claimed CYP450s to be the main mechanism providing resistance against type Ⅰ and type Ⅱ pyrethroids[28]. In other studies, CYP450s along with other detoxifying enzyme classes *i.e.* GSTs and/or CCEs are reported to confer reduced susceptibilities against SPs[42]. Enhanced activities of all the above-mentioned enzyme classes have been found to provide resistance against deltamethrin[42]; similar inferences were made on deltamethrin resistant population of *Ae. aegypti* from Chile, where CYP450s, CCEs, and GSTs provided the resistance (Table 1). In an Indonesian population of *Ae. aegypti*, CYP450s and β-CCEs provided a significant level of resistance against permethrin[48].

Most frequently, deltamethrin resistance is conferred by GSTs and CYP450s[74].

Different classes of detoxifying enzyme groups together or alone have been shown to provide pyrethroid resistance against different populations of *Ae. aegypti*. In many studies, CCEs were shown to provide varying patterns of resistance against pyrethroid insecticides, *i.e.* deltamethrin[43], lambdacyhalothrin[70]. In another study, CCEs along with GSTs were reported to be elevated in pyrethroid-resistant populations of *Ae. aegypti*[84]. The same combination of enzymes was also involved in cypermethrin resistant wild populations of *Ae. aegypti*[71]. However, some reports completely discourage the involvement of metabolic detoxification in resistance against SPs[69].

Although, metabolic detoxification has been actively linked to SP resistant populations, yet the role of target-site resistance is more pronounced than the former in *Ae. aegypti*. Target site alteration alone or along with metabolic detoxification has been shown to confer pyrethroid resistance in *Ae. aegypti*. In a deltamethrin and permethrin resistant population of *Ae. aegypti*, both elevated activities of GSTs and CCEs along with a frequent V1016I (80% prevalent) and F1534C (lesser) kdr mutation were observed[20].

Some advanced studies have summarized that in *Ae. aegypti*, resistance against deltamethrin is provided metabolically through an overexpressed GST (specifically GSTe2) and genetically through spread of kdr mutations, *i.e.* V1016I and F1534C[21]. Moreover, CYP450s were reported to provide OP resistance only[21]. In a Chilean population of *Ae. aegypti*, kdr mutation I1016 was found to provide resistance against four pyrethroid insecticides, namely, deltamethrin, lambdacyhalothrin, permethrin, and cyfluthrin[35]. A strong correlation has also been observed on kdr mutations Ile1016 and Cys1534 with high to moderate deltamethrin resistance[11].

Against permethrin, the sole type Ⅰ pyrethroid is still in use, kdr mutation and elevated activities of α-CCEs played the main role[89]. Prevalence of kdr F1534C has been reported to play a major role in a permethrin resistant Indian *Ae. aegypti* population[84]. Some studies report that in the majority of *Ae. aegypti* population, metabolic detoxification has a very minor role in pyrethroid detoxification, rather it is kdr mutation that has the main role[84,87]. Similar observations have been made on the efficacy of kdr mutation F1534C and V1016G in imparting permethrin resistance in *Ae. aegypti*[90].

Studies have also been made on the extent of resistance made by different kdr mutations. Kdr mutation F1534C was found to be more predominant than V1016I in a deltamethrin resistant population of *Ae. aegypti*[91]. The scenario may be that the deltamethrin exposure may have provided a strong selection pressure and individuals with F1534C mutation possessed survival advantage over individuals with V1016I. In another study by the same author, opposite results were observed[92]. The kdr F1534C has been shown to provide moderate resistance against deltamethrin[28,38] and the presence of V1016G along with the above mutation had an additive effect on pyrethroid-resistant population of *Ae. aegypti* in Malaysia[28].

However, populations of *Ae. aegypti* mosquitoes with similar prevalence of kdr mutations yet varying degrees of insecticide resistance have been observed in nature, which indicates the dependency of observed resistance on metabolic detoxification (by GSTs, CYP450s, and CCEs alone or in combination)[93]. Through expression of CYP450 proteins in *Escherichia coli*, it was found that CYP9J32, CYP9J24, CYP9J20, and CYP9J28 could detoxify deltamethrin[94]. Moreover, CYP9J32 showed the greatest ability to metabolize deltamethrin but weak for permethrin detoxification capability[94]. The other three CYP450s enzymes also possessed the ability of pyrethroid detoxification but at a lower rate[94]. In another study, deltamethrin resistant *Ae. aegypti* population exhibited up-regulated CYP9M9 and GSTE7[42].

The role of the above-mentioned mechanisms alone or in combination has been found to provide resistance against SPs in different wild populations of *Ae. aegypti*; however, the exact mechanism is not known. The best theory seems to be the role of both mechanisms in a different field population of *Ae. aegypti* as has been observed by Marcombe *et al.*, where both metabolic detoxification (through CYP450s, CCEs, and GSTs) along with kdr mutations, *i.e.* V1016I jointly provided resistance against pyrethroids[42].

3.1.4. Resistance against CBs

Ae. aegypti populations resistant against carbamates have been reported throughout the Asian and African continent (Table 1). Resistance against bendiocarb was reported from Pakistan, Malaysia, Nigeria, Mexico, China, and Saudi Arabia, whereas, propoxur resistance was reported from India, Cote d'Ivoire, Nigeria, Malaysia, Senegal, and China. Very scanty studies have been conducted since 2012 to unveil the mechanism conferring resistance against carbamates. CCEs have long been reported to have a secondary role in conferring resistance against carbamates[95]. Bendiocarb resistance was found to be provided by enhanced activities of CYP450s in Malaysian *Ae. aegypti* population[28]. However, CYP450s could account only for a proportion of total observed resistance against bendiocarb[28]. Lowered levels of AchE were found to provide resistance against propoxur in another population of *Ae. aegypti*[26]. Though the exact mechanism providing CB resistance is yet not revealed, the role of metabolic detoxification seems to be the dominant mechanism owing to the availability of more such reports throughout the world.

3.2. Insecticide resistance in Ae. albopictus

Ae. albopictus has very recently emerged as the potential dengue and chikungunya vector[3]. Increased expansion of *Ae. albopictus* due to globalisation has increased the risk of disease transmission through this vector worldwide[3]. However, very few literatures exist on the status and mechanisms of insecticide resistance of *Ae. albopictus*. In most of the conducted studies, this species has been found to be more susceptible to insecticides as compared to *Ae. aegypti* (Figure 3). Each pie in Figure 3 represents the contribution of that particular insecticide towards the studies resistance/incipient resistance or susceptibility. The resistance against DDT seems to be omnipresent throughout different wild populations of *Ae.*

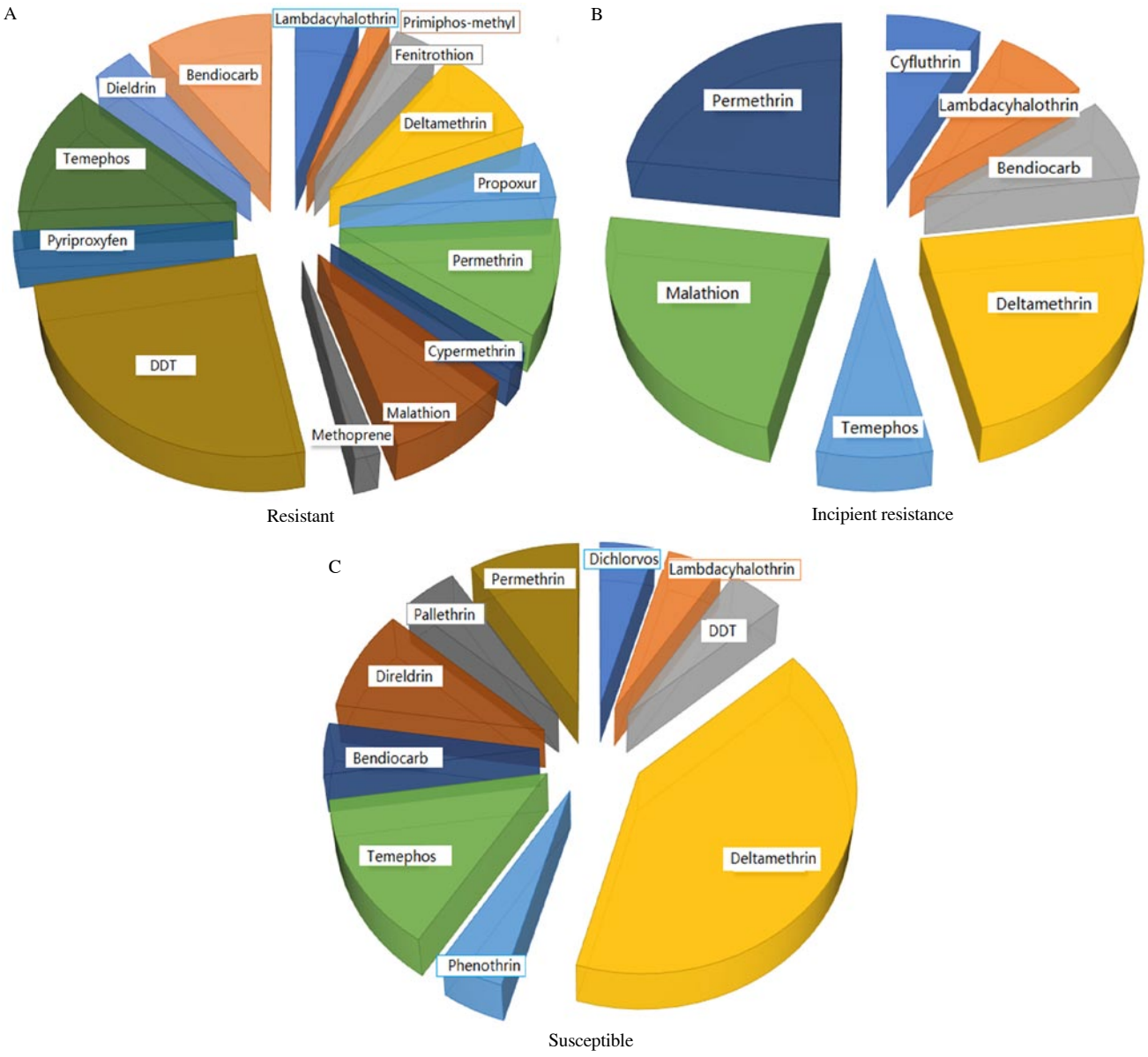

Figure 3. Proportion of resistant, susceptible, and incipiently resistant *Aedes albopictus* mosquitoes reported throughout the world.

albopictus (Figure 3A and Table 2). Similarly, maximum cases of incipient resistance were noted against deltamethrin, permethrin and malathion (Figure 3B). The maximum cases of susceptibility in *Ae. albopictus* mosquitoes were noted against deltamethrin (Figure 3C). *Ae. albopictus*, an anthropophobic and exophilic species by nature, has varying trends of insecticide resistance compared to *Ae. aegypti* due to differences in their preferential resting sites[96].

DDT resistant strains of *Ae. albopictus* have been seen to occur in Sri Lanka[12], India[37,76,77] Cameroon[39], United States of America[78], Pakistan[31,33] and Central Africa[26]. In *Ae. albopictus*, detoxification through enhanced activities of GSTs alone[78] or by a combination of both GSTs and α-, β-CCEs may be accounted for resistance against DDT[76]. Moderate resistance to dieldrin has also been observed in the Malaysian population of *Ae. albopictus*[28].

Both temephos resistant and susceptible strains of *Ae. albopictus* have been found throughout the world. Temephos have been found to be very efficient in control of some of the *Ae. albopictus* larvae in many studies[77,78]. However, low to moderate resistances have been noted against temephos in different field populations of *Ae. albopictus*[7,33,37]. Enhanced activities of CCEs alone[7] or GSTs and CCEs together[26] have been found to be the underlying mechanism providing altered susceptibility to temephos in *Ae. albopictus*. Resistance to temephos has also been shown to be mediated through the upregulation of two CCEs, *i.e. CCEae3a* and *CCEae6a* through gene amplification[97,98]. Same candidate genes have also been shown to perform similar functions in *Ae. aegypti*. Malathion has been used for a long time throughout the world as a part of mosquito control programmes. This fact is well reflected by the reports of malathion resistant wild populations of *Ae. albopictus* (Table 2). Metabolic detoxification through β-CCEs was found to be the main mechanism providing malathion resistance[78].

Scanty reports have been made on pyrethroid resistance in *Ae. albopictus*. Many studies showed the prevalence of high susceptibility levels of different field populations of *Ae. albopictus* to synthetic pyrethroids[7,28,37,76–78]. Still *Ae. albopictus* possessing an altered susceptibility to permethrin has been noted in many parts of the world[12,33]. However, *Ae. albopictus* population moderately resistant

to permethrin was observed in Malaysia where part of the observed resistance was contributed by detoxification through CYP450s[28]. Wild populations of *Ae. albopictus* resistant to the majority of the commonly used synthetic pyrethroid insecticides, *i.e.* deltamethrin, lambdacyhalothrin, and permethrin have been found in Pakistan[31]. Elevated activity of enzymes has been correlated with resistance to deltamethrin[26]. More reports exist on metabolic detoxification of insecticides than target site mutations, *i.e.* presence of kdr mutations for *Ae. albopictus*.

Carbamate resistant strains of *Ae. albopictus* have been found in Malaysia, Pakistan, and Nigeria (Table 2). Resistance to bendiocarb has been found to be mediated through the detoxifying activities of CYP450s[28]. However, resistance to propoxur has been indicated to be provided by altered AchEs in other population of *Ae. albopictus*[26]. *Ae. albopictus* larvae significantly resistant to propoxur has also been noted in field populations of Martinique island[78]. More advanced studies and worldwide surveys on the level of insecticide resistance prevailing in different populations of *Ae. albopictus* should be conducted for a deeper understanding of insecticide resistance and mechanisms in *Ae. albopictus*.

4. Conclusions

The phenomenon of insecticide resistance in mosquitoes has been studied in great detail throughout this decade. Advancements in the form of more sophisticated and precise instruments along with discovery of novel molecular techniques have resulted in increased knowledge on the mechanisms of insecticide resistance occurring in nature. However, the phenomenon of insecticide resistance seems to be mediated by a combination of different mechanisms rather than any single or specific mechanism. Metabolic detoxification through different enzyme groups (CCEs, CYP450s, and GSTs) has been found to be the major resistance-conferring mechanism against all the four insecticide groups in *Ae. albopictus*. In *Ae. aegypti* for OCs, OPs and CBs, it was detoxification system that provided resistance whereas for SPs it was mainly a combination of both detoxification and kdr mutations.

More research experiments should be targeted on the accurate identification of up-regulated detoxification genes in insecticide-resistant populations of *Aedes* mosquitoes. Scientific studies should also be carried out to identify the known as well as novel kdr mutations imparting resistance phenomenon to field populations of *Aedes* mosquitoes worldwide. In this context, data on *Ae. albopictus* is very limited, so more and more experiments should be directed on *Ae. albopictus* for identification of mechanisms conferring resistance to them. The concept of a fixed recommended insecticide dose for mosquitoes throughout different geographical location seems misleading, so the prevailing level of susceptibility/resistance to insecticides should be brought into use to devise the area-specific dosage of insecticides for effective vector control. Also, the knowledge gained through the study of mechanisms conferring insecticide resistance should be used to halt, delay, or manage the level of insecticide resistance. Scientific studies to find out the ways to delay the onset of resistance should be conducted. Also, search for ideas and concepts for environmentally safe vector control strategies should be devised, such as mosquito control through botanicals, use of sterile male mosquito technology, discovery of a novel group of mosquitocidal compounds with different targets of actions. Lastly, for effective prevention of the disease, involvement of mass/community in source reduction activities and environmental management is inevitable. People should be aware of the consequences of unchecked use of insecticides and they should be encouraged to take part in vector control programmes for efficient mosquito management.

Conflict of interest statement

We declare that there is no conflict of interest.

Acknowledgements

We would like to express our sincere thanks to the Head, Department of Zoology, University of North Bengal, for providing laboratory facilities and funds from the departmental budget allocation. We also express our sincere appreciation to those scientists and authors upon whose concepts and scientific contributions the present work has been analysed and reviewed. Gratitudes are also expressed to the University of North Bengal for providing uninterrupted Local Area Network that has helped immensely in searching and collecting the literature related to the topic. Thanks are being extended to fellow laboratory workers for their help whenever needed.

Funding

The first author expresses sincere gratitude to University Grants Commission, New Delhi, India for providing financial assistance throughout this work through Junior Research Fellowship [award letter Sr. No. 2121430414, Ref No. 21/12/2014 (ii) EU-V, Dated 03/06/2015].

Authors' contributions

DS conceived the concept of the study. MB performed literature search and data collection and analysis. DS and MB contributed to data interpretation. MB drafted the manuscript and DS revised the manuscript critically.

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