ASSESSING THE INSECTICIDE RESISTANCE STATUS OF *AEDES AEGYPTI* TO DELTAMETHRIN IN SOUTHERN GHANA

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ABSTRACT

Aedes aegypti mosquitoes are the vectors of several important human infections including dengue, chikungunya, and yellow fever, which affect hundreds of millions of people each year globally in tropical and subtropical regions, causing a burden of disease equal to more than four million disability-adjusted life years in 2013. Vector control remains a key component in preventing these illnesses, and pyrethroid insecticides have been among the most widely used vector control tools because of their efficacy and favourable mammalian toxicity profile. However widespread use of these insecticides has led to increasing resistance to some or all pyrethroids in many Aedes populations. Deltamethrin is among the six pyrethroids insecticides recommended by the World Health Organization in the framework of the WHO pesticides evaluation scheme for the treatment of mosquito nets and is among the type II pyrethroids with high toxicity. Though, deltamethrin has been found an effective larvicide and adulticide against mosquitoes, various authors have reported the development of resistance against deltamethrin in these mosquitoes. This study aimed to assess the resistance status of *Aedes aegypti* to deltamethrin in Southern Ghana. Mosquito larvae collected from the three study sites; Cape Coast, Takoradi and Tema were reared in an insectary. Standard WHO bioassays using insecticide-treated filter papers were conducted on a total of 995 *Aedes aegypti* mosquitoes. The mortality rates recorded across the sites were 80%, 86.6%, and 57.8% in Cape Coast, Takoradi and Tema respectively. Phenotypic resistance was determined with WHO susceptibility tests and *Aedes aegypti* were found to be highly resistant to Deltamethrin. This urges immediate attention to the investigation of the mechanisms used to resist such high

toxicity of Deltamethrin and appropriate vector control strategies for arboviral disease control in Southern Ghana.

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CHAPTER ONE

INTRODUCTION AND LITERATURE REVIEW

Mosquitoes are the most important group of insects with regard to public health. They are responsible for the transmission of many medically important pathogens and parasites such as viruses, bacteria, protozoans, and nematodes, which cause serious diseases such as malaria, dengue, yellow and chikungunya fever, encephalitis or filariasis (Beaty and Marquardt 1996; Eldridge and Edman 2000). The Aedes mosquitoes are the carriers of many arboviral diseases including dengue, chikungunya, zika, yellow fever and Rift Valley disease. These mosquitoes live in tropical, subtropical and temperate climates and were spread as a result of centuries of shipments (Powell et al., 2018).

They are identified by the distinctive black and white markings on their bodies and legs and unlike other mosquitoes, they are active and bite only during the daytime, with peak activity during the early morning and in the evening before dusk. There are two specific species of Aedes that are important transmitters of viruses and they are *Aedes aegypti* and *Aedes albopictus*. *Aedes aegypti*, commonly referred to as the yellow fever mosquito is found in urban areas and prefers human blood as its main source of feed while *Aedes albopictus* known as the Asian tiger mosquito feeds both on humans and animals and is found primarily outdoors (Joannides et al., 2021). *Aedes aegypti* takes refuges in dark recesses indoors (endophilic) and uses a variety of containers both indoors (e.g., water-storage containers, flower pots) and around the home (e.g., wells, discarded containers, tyres, plant saucers). They are known to be invasive and have expanded to several new regions relatively recently (Demok et al., 2019). *Aedes aegypti* mosquitoes are the vectors of several important human infections which affect hundreds of millions of people each year globally in tropical and subtropical regions, causing a burden of disease equal to more than four million disability-adjusted life years in 2013 (Natalie M. Bowman. et al.2018). Available data indicate that in recent years there have been dengue and Chikungunya outbreaks in the West Africa subregions, in countries including Cote d'Ivoire, Burkina Faso, Gabon, Senegal, and Benin (Abdulai et al., 2023). Geographical expansion of Aedes Aegypti has fostered the incidence of dengue fevers to gain an apparent increase worldwide, which put half of the world's population at stake for the disease (Amelia-Yap et al., 2018). Furthermore, exposure to dengue and Chikungunya virus has been established in Ghana via immunological surveys (Abdulai et al., 2023). Although there is currently no evidence indicating outbreaks of dengue in Ghana, there is a high risk due to the closeness and high density of the Aedes mosquito population in the country. Their ability to regulate the ionic and water composition of their hemolymph is a major physiological phenomenon, allowing the mosquito to adapt to a range of ecological niches. This behaviour enormously complicates its control (Jeffery et al.2018).

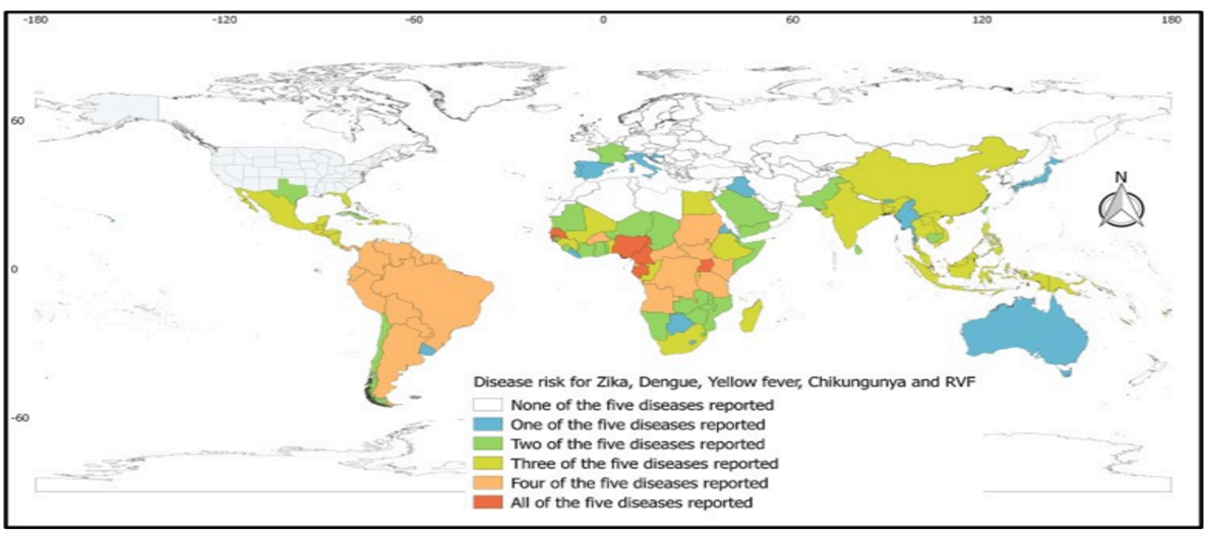

Figure 1: Global country-level occurrences of selected arboviral diseases(Leta et al., 2017).

Aedes-borne arboviral diseases are a growing public health concern, but their control and prevention have received limited attention in Ghana in Africa. It has been suggested that Africa could experience a shift in vector-borne disease from malaria to arboviruses because of the effects of warming temperatures as a result of climate change (Abdulai et al., 2023). Evidence for this comes from the growing number of arboviral outbreaks such as yellow fever and dengue fever reported in West Africa in the last 5 years (Abdulai et al., 2023). Ghana has a long history of yellow fever epidemics with the most recent outbreak reported in October 2021. Recently, dengue virus was detected in suspected malaria and Ebola patients in Ghana. (Abdulai et al., 2023). The expansion of the cases could be associated with the excellent adaptation of the vector to tropical areas, with the existing faults in mosquito control, and with the poor participation of people from local communities in strategies to protect themselves (Duque, Navarro-Silva, & Trejos, 2009). An effective vector prevention to transiently remove *Aedes aegypti* involves several strategies such as eliminating potential mosquito breeding sites, applying chemical insecticides and biological control (the use of natural enemies). However, the most extensively practical control for *Aedes aegypti* owing to its high efficiency in regulating the population with relatively rapid action is the application of chemical insecticides. The use of multiple classes of synthetic insecticides has been largely practised in vector control strategies, with pyrethroid- based formulations massively dominating the insecticides market worldwide (Amelia-Yap et al., 2018). Pyrethroids are neurotoxins which modify the normal function of insects and cause disruption in the Voltage-sensitive sodium channel gene by depolarizing neurons, paralyzing and eventually killing the insect. Deltamethrin, cypermethrin, cyfluthrin, lambda-cyhalothrin, permethrin, alpha-cypermethrin, cyfluthrin pyrethrum, bifenthrin, d-phenothrin, z-cypermethrin and etofenprox are the major types of pyrethroids used (Amelia-Yap et al., 2018), and that their treatment is either residual/space spray. Pyrethroids are the predominant insecticides for vector control because of their low toxicity to humans and low cost (Chen et al.2018). The use of these insecticides however has caused the mosquitoes to develop resistance (Amelia-Yap et al., 2018).

Widespread, intensive insecticide use for mosquito control has allowed genetic mutations, causing subsequent resistance to future chemical exposure. *Aedes aegypti* are efficient vectors because they have adapted to living their entire life cycle in close proximity to humans (Joannides et al., 2021). They are well adapted to urban habitats, and as a result, are usually more likely to be exposed to insecticides and develop resistance than *Aedes albopictus* (Vontas et al., 2012). Several possible adaptations permit the mosquito to survive doses of an insecticide, usually classified based on their biochemical or physiological properties as either mechanisms of decreased response to the insecticides or mechanisms of decreased exposure (Kioulos et al., 2014). Resistance to Aedes mosquitoes has been reported in several West African countries including Burkina Faso, Cameroon, Senegal and Ghana (Abdulai et al., 2023). In Ghana, the resistance profile of *Aedes aegypti* mosquitoes to major insecticides used for public health varied (Abdulai et al., 2023). A recent report indicates that *Aedes aegypti* are resistant to DDT and pyrethroids, deltamethrin and permethrin in all the studies (Abdulai et al., 2023). Also, the study showed moderate to high phenotypic resistance among *Aedes aegypti* populations across the study sites. Evidence of pyrethroids resistance in *Aedes aegypti* was also established in other previous studies from Ghana and other

African countries. However, what is driving insecticide resistance in these populations is still uncertain.

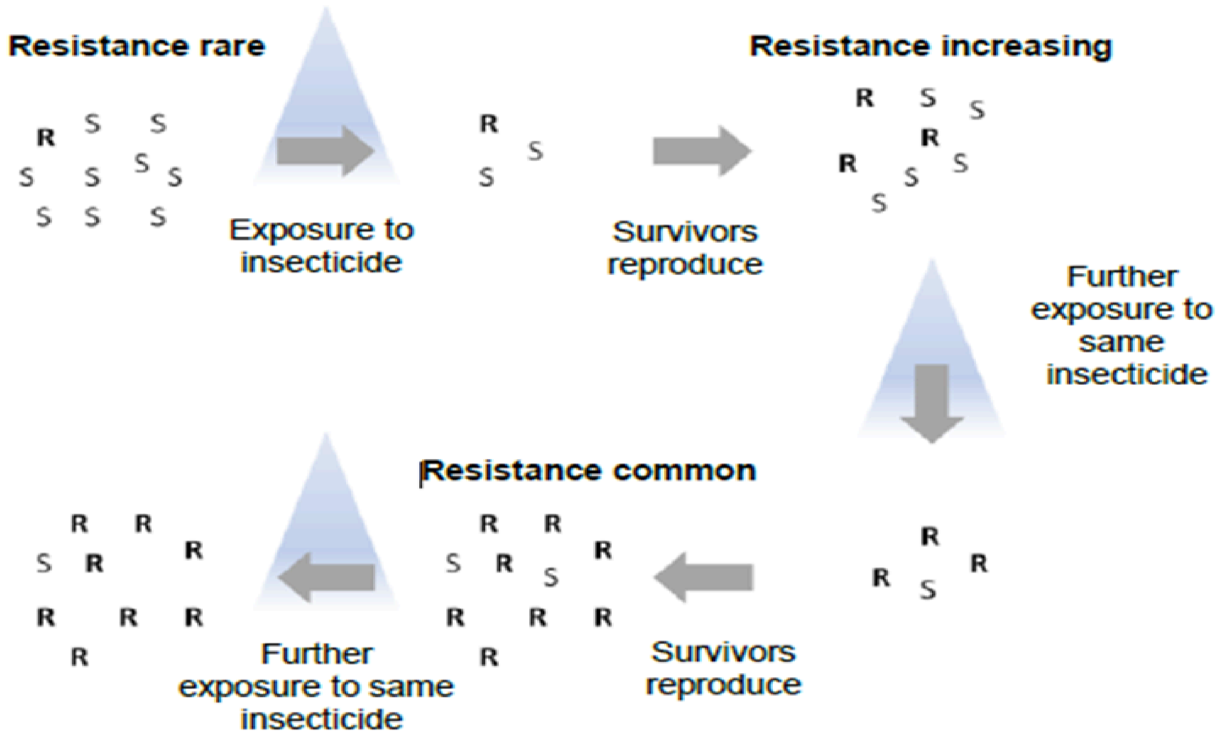

Figure 2; Insecticide resistance development in a mosquito population (Corbel & Guessan, 2013)

Mechanisms of resistance implicated in Aedes worldwide usually involve target-site mutations and metabolic detoxification (Abdulai et al., 2023). Many target-site knock-down resistance (kdr) mutations have been identified as resistance markers in Aedes mosquitoes globally (Pareja-Loaiza et al., 2020). Three kdr mutations have been detected in the African Aedes population so far, V410L, V10161 and F1534C. In Ghana two of these mutations (V10161 & F1534C) have been found to cause resistance to pyrethroids with F1534C being the most common (Lopez-Monroy et al., 2018). The kdr mutation V410L causes reduced sensitivity to pyrethroids and was recently reported in Aegypti from Burkina Faso and Cote d'lvoire (Abdulai et al., 2023). The involvement of detoxification enzymes in resistance has been established by several studies in Africa, commonly via the use of synergists (e.g., PBO) which elevate insecticide mortality (Su et al., 2019). Piperidyl butoxide (PBO) primarily inhibits the cytochrome P450 monooxygenase superfamily of enzymes, members of which are frequently implicated in the (pyrethroid) in mosquitoes. PBO has been found to restore the susceptibility of several African Aedes populations to insecticides (Maestre-Serrano et al., 2023). Other pyrethroid resistance mechanisms include Physiological and behavioural avoidance, and cuticular resistance. Cuticle thickening is implicated in insecticide resistance by reducing the uptake of the insecticides that reach the target site in response to the modification of the chemical composition of the cuticle (Amelia-Yap et al., 2018). The fact that this least understood mechanism may play a substantial role in resistance urges immediate attention to investigation particularly in pyrethroid-resistant *Aedes aegypt*i.

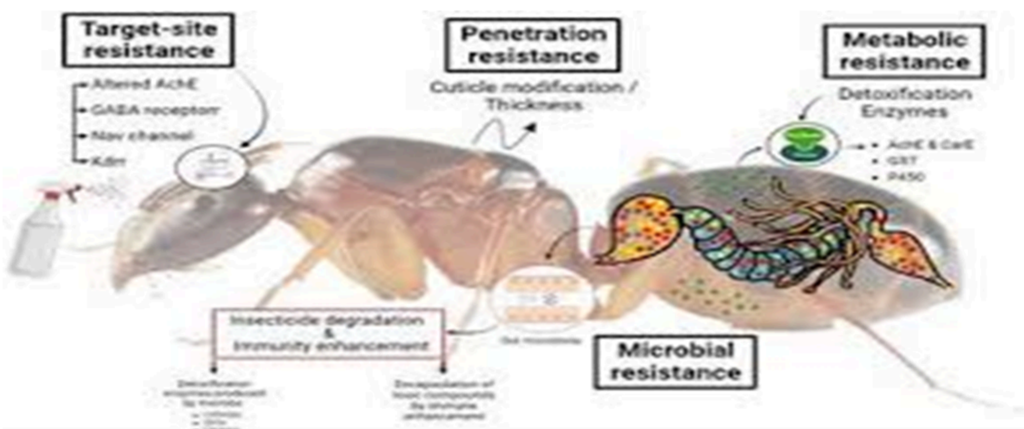

Fig 3*: A schematic diagram represents the role of enzymes and gut microbiota in pesticide detoxification in insects. (Junaid et al.2023)*

Deltamethrin is among the six pyrethroids insecticides recommended by the World Health Organization in the framework of the WHO pesticides evaluation scheme for the treatment of mosquito nets (Sarita et al. 2011). Deltamethrin belongs to the sub-group of pyrethroids containing an alpha cyano-group in their chemical structure and is extremely potent against insects even at much lower concentrations (Chrustek et al., 2018). The neurotoxic activity of deltamethrin is connected with the prolonged opening of the voltage-gated sodium channels which results in membrane depolarization of neurons, repetitive discharges and synaptic disturbances leading to hyperexcitatory symptoms of poisoning in insects. It also influences the function of the chloride and calcium channels of the neuron. According to results from a report, deltamethrin was found to be highly effective against the adult *Aedes aegypti* as 50% of the adult mortality was obtained in only 4.5 minutes. The selection pressure of deltamethrin exerted at the adult stage of *Aedes aegypti* caused only a slight increase in the levels of resistance (Sarita et al. 2011). Though deltamethrin has been found an effective larvicide and adulticide against mosquitoes, various authors have reported the development of resistance against deltamethrin in these mosquitoes. In this proposal, we will explore the resistance status of *Aedes aegypti* to a commonly used insecticide, such as deltamethrin in southern Ghana and potential strategies for controlling their populations in areas where the resistance is high. This is to help make data-driven policy decisions to reduce the increasingly widespread of *Aedes aegypti* in areas where deltamethrin resistance is high.

Fig 4; A map showing the spread of resistance in Aedes aegypti to Deltamethrin in West African Countries.

Aim

To assess the resistance status of Aedes mosquitoes to deltamethrin in Southern Ghana and identify effective control measures.

Objectives

1. To examine the resistance rate of Aedes mosquitoes to deltamethrin within Southern Ghana.
2. To compare the resistance status of Aedes mosquitoes in the three regions within Southern Ghana

CHAPTER TWO

MATERIALS AND METHODS

Study Area

The study was carried out in three sites in the southern parts of Ghana, from which larval collections were made during the rainy season from April to July 2023. The sites were Cape Coast (5.1315ºN, 1.2795ºW), Takoradi (4.9016ºN, 1.7831ºW), and Tema (5.7348ºN, 0.0302ºE). Cape Coast; fishing port, and the capital of Cape Coast Metropolitan District and Central Region of Ghana. It is located in southern Ghana and 165 km west of Accra the capital of Ghana. Takoradi lies on the south-western coast of Ghana and is the smallest half of the twin city Secondi-Takoradi, which is the capital of the Western Region. It is famous for being the home of Ghana's first deep-water seaport. Tema is a coastal city in Ghana located in the neighbourhood of Accra, right on the Atlantic coast. It is a developing business city, with a large port and excellent transportation communication. In all three sites, the fundamental job for the local residents is fishing, where car tyres are imported thus facilitating the importation of Aedes mosquitoes.

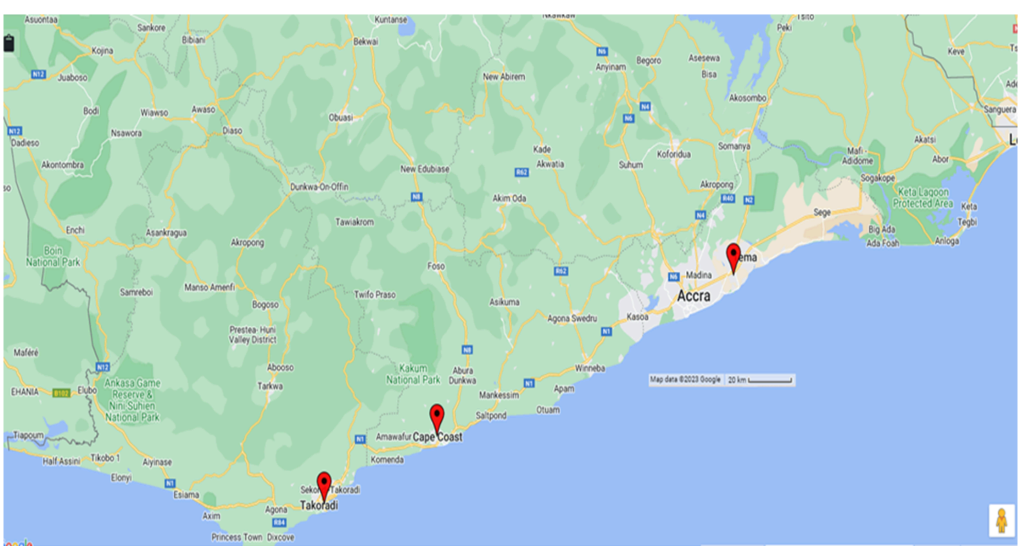

Fig 5. A map showing the study sites

Collection localities of the *Aedes* Larvae

Figure 6: Breeding containers at breeding localities

Collection and rearing of mosquito larvae

Water containing the mosquito larvae in the containers was scooped with the help of a dipper and poured into PET plastic containers. The Aedes mosquito larvae collected were transported in well-labelled plastic bottles to the insectary. Larvae were reared in different plastic trays to prevent the crowding of larvae in one tray. Larvae were fed with fish meal until they developed into pupae. Pupae were removed daily with a pipette into small rubber bowls and placed in a Bug Dorm-1 cage for emergence. Adults were provided with 10 % sugar solution. The temperature and humidity in the laboratory were monitored regularly using a thermo-hygrometer.

Adult susceptibility bioassay

Adult susceptibility tests were carried out using the WHO standard procedures and test kits for adult mosquito susceptibility tests. A WHO bioassay test paper impregnated with 0.05% Deltamethrin (Pyrethroid) was used for the bioassay. Only non-blood fed 3–5 days old adult females were used for the susceptibility test (WHO, 2016). Five bioassay kits were used to run the test for the insecticide. Four of the bioassay kits were lined with impregnated insecticide papers while one kit was lined with a clean white paper as a control test. A total of 125 mosquitoes were used for the tests. An aspirator was used to transfer 25 mosquitoes from the cages into the holding tube through the filling hole in the slide. The mosquitoes were then transferred into the exposure tubes through a hole in the lid that separates the holding tube and the exposure tube. The bioassay kits were then set in an upright position with the mesh screen on top for one hour. After one hour, mosquitoes were then carefully transferred back into the holding tube for a recovery period of 24 hours during which they were fed with 10% sugar solution. After 24 hours each bioassay kit was opened and the number of mosquitoes either knocked down or still alive were recorded for the calculation of their mortality.

Calculation of mortalities and corrected mortalities

The mortality of the test samples for the insecticide used was calculated by summing the number of dead mosquitoes and then expressing this as a percentage of the total number of exposed mosquitoes (WHO, 2016).

$$Observed\ mortality = \frac{Total\ number\ of\ dead\ mosquitoes}{Total\ sample\ size} \times 100$$

A similar calculation was made to obtain a value for the control mortality. When the control mortality was ≥20%, the test was discarded. When control mortality is <20%, then the observed mortality was corrected using Abbott’s formula

$$Corrected\ mortality = \frac{\%Observed\ mortality - \%\ Control\ mortality}{100 - \%Control\ mortality} \times 100$$

If the control mortality is <5%, no correction of test results was necessary, whereas mortality of ≥5% requires correction.

Data Analysis

Percentage mortality of each region was calculated after the 24-hour recovery and bioassay results were reported as proportions of dead mosquitoes with 95% confidence intervals. The mortality rate in each region was <5%, hence required no correction. The resistance status of *Aedes aegypti* mosquitoes was determined according to WHO criteria for interpreting susceptibility test results (WHO, 2016). Mortality rates greater than or equal to 98% indicate susceptibility, while mortality rates less than 98% indicate resistance. Mortality rates that fall between 90 and 97% indicate possible resistance. A Chi-square test was used to determine if there was any significant difference among the mortalities of *Aedes aegypti* observed in the regions.

CHAPTER THREE

RESULTS

Distribution of Larvae

A total of 995 *Aedes aegypti* larvae were collected from the breeding containers. Out of the three collecting localities, the total number of mosquitoes accounted by Cape coast, Takoradi and Tema were found to be 300, 355, and 340 respectively (Table 1).

Table 1: Number of *Aedes aegypti* larvae collected from the three regions

Locality	**Number of mosquitoes**
Cape coast	300
Takoradi	355
Tema	340
Total	995

Adult Susceptibility Test

The mortality rate for Cape Coast, Takoradi and Tema was 88%, 86.6% and 57.8% (Table 2, Table 3 and Table 4) respectively. According to WHO (2013), mortality rates less than 90 % indicate resistance. Therefore, 88%, 86.6% and 57.8% mortality to Cape Coast, Takoradi and Tema respectively, indicates that *Aedes aegypti* is resistant to Deltamethrin.

Table 2: Bioassay results for Cape coast using Deltamethrin 0.05%

Test number	Dead mosquitoes after recovery period	Alive mosquitoes after recovery period	Total number of mosquitoes	Observed Mortality (%)
I	19	2	21	88.0
II	21	3	24	
III	21	4	25	
IV	20	2	22	
control	0	25	25	0
Total	81	36	117	

Table 3: Bioassay results for Takoradi using Deltamethrin 0.05%

Test number	Dead mosquitoes after recovery period	Alive mosquitoes after recovery period	Total number of mosquitoes	Observed Mortality (%)
I	26	3	29	86.6
II	23	5	28	
III	25	3	28	
IV	23	4	27	
control	0	25	25	0
Total	97	40	137	

Table 4: Bioassay results for Tema using Deltamethrin 0.05%

Test number	Dead mosquitoes after recovery period	Alive mosquitoes after recovery period	Total number of mosquitoes	Observed Mortality (%)
I	13	15	28	
II	16	12	28	

III	17	9	26	57.8
IV	17	10	27	
control	0	25	25	0
Total	63	71	134	

Table 5: Mortality rate of each region

Regions	**Mortality rate (%)**
Cape coast	88.0
Takoradi	86.6
Tema	57.8

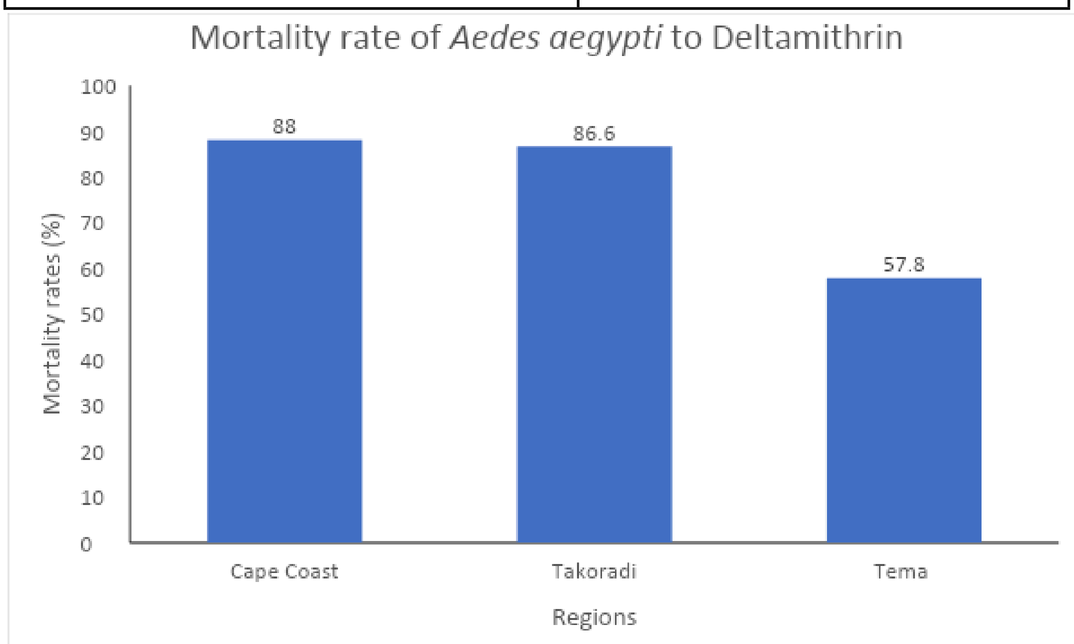

Fig 7: A bar chart showing the Mortality rates of Aedes aegypti to Deltamethrin in the three regions

Chi-square tests of independence were performed to determine if there is any significant difference among the mortalities of the three regions to Deltamethrin. With a chi-square (x^2) of 1.45807 and a degree of freedom of 2, the test showed a P-value of 0.48237 which is greater than the alpha value (>0.05). A P-value >0.05 indicates that there is no significant difference among the mortalities. A Chi-square contingency table was calculated to provide a foundation for the Chi-square test (Table 6)

Table 6: Contingency results from Chi-square test at 95% confidence interval

Regions	Dead mosquitoes		Alive mosquitoes		Total
	Observed	Expected	Observed	Expected	
|Cape coast	81	70.84	11	21.16	92
Takoradi	97	86.24	15	25.76	112
Tema	63	83.93	46	25.07	109
Total	241		72		313

CHAPTER FOUR

DISCUSSION

Insecticide resistance is compromising the control of arboviral diseases around the globe, but the resistance status of *Aedes aegypti* mosquitoes in Africa is poorly defined (Badolo et al., 2019). This study provides evidence of the resistance of *Aedes aegypti* populations in Ghana to a public health insecticide which is among the type II pyrethroids with high toxicity (Deltamethrin). The number of mosquitoes collected from their breeding habitats, mainly abandoned car tyres were highest in Takoradi (355), followed by Tema (340), then in Cape coast (300). The high breeding rate of *Aedes aegypti* in discarded tyres shows how favourable the tyres are for the laying of eggs by adult Aedes mosquitoes. Most of the mosquitoes that were randomly sampled were found to be *Aedes aegypti* and based on surveillance data obtained, *Aedes aegypti* was the most common species across six regions in Ghana (Amoa-Boompem et al 2016). *Aedes aegypti* was the predominant species (75.5%) in an urban site, Accra, according to a study by (Suzuki et al 2016). therefore, multiple studies enable the conclusion that *Aedes aegypti* is the dominant vector in urban and suburban areas in Ghana (Abdulai et al., 2023). Overall, the resistance profile of *Aedes aegypti* mosquitoes to the insecticide (Deltamethrin) used for public health varied across sites with Cape coast, Takoradi, and Tema having 88.0%, 86.6%, and 57.8% respectively.

Out of the three regions, Takoradi recorded the highest mortality rate (86.6%), followed by Cape coast (80%) and then Tema (57.8%). A Chi-square tests of independence were performed to determine if there is any significant difference among the mortalities of the three regions to deltamethrin and from the tests, (x^2 =1.45807, df = 2, p-value =0.48237, alpha level =0.05), it showed that there is no significant difference thereby failing to reject the null hypothesis. Pyrethroids (Deltamethrin) resistance in *Aedes aegypti* populations were observed across the sites and evidence of this resistance were established in other previous studies from Ghana and other African countries. According to WHO (2013), mortality rates less than 90% indicates resistance hence *Aedes aegypti* in Tema were more resistant to deltamethrin than A. aegypti in Cape coast and Takoradi. This result corroborates previous studies from Thailand and Benin that reported high resistance to deltamethrin and permethrin in *Aedes aegypti*. A study conducted in Southern Benin by (Alphonso et al. 2023) showed full susceptibility of Aedes aegypti to bendiocarb in all the surveyed communes and hence suggested that bendiocarb could be a good candidate for an effective control of pyrethroid resistant-Aedes vector population. However, a work by (Abdulai et al.2023) gave a different result where *Aedes aegypti* in Tema were found to be resistant to Bendiocarb. This may be due to the fact that Tema with its large port and excellent transportation communications is a developing business city, hence the mosquitoes may have been frequently exposed to the insecticide making them less sensitive to the insecticides' effect. Takoradi showing the least resistant may be attributed to the fact that the rate of insecticide usage is low. Resistance to a given insecticide usually confers resistance to the other insecticides in the same class, and may also confer cross-resistance to one or more other classes of insecticide (Corbel & N' Guessan, 2013). Therefore, resistance to pyrethroid (Deltamethrin) generally confers cross-resistance to other insecticides, and that limits the choices of effective insecticides (Moyes et al., 2021). The resistance of *Aedes aegypti* to Deltamethrin and other pyrethroids were also discovered by (Sombié et al.2019), who concluded that WHO bioassays revealed that the local *Aedes aegypti* populations from Somgandé (Burkina Faso) were highly resistant to pyrethroids, with mortalities of 15% for permethrin and 37% for deltamethrin, although the work of (Ocampo et al. 2011) gave a contrary result. The work of (Ocampo et al., 2011). showed that *Aedes aegypti* mosquitoes collected in all the surveyed communes in Colombia with endemic dengue transmission were susceptible to deltamethrin and permethrin. This proves that Deltamethrin resistance is increasing in Aedes populations.

Deltamethrin belongs to the sub-group of pyrethroids containing an alpha cyano-group in their chemical structure and is extremely potent against insects even at much lower concentrations (Chrustek et al., 2018). Hence for *Aedes aegypti* to develop a resistance may be attributed to the excessive use of the insecticide in controlling Aedes vector since Pyrethroids are most often used in Ghana for vector control programs (Baffour-Awuah et al., 2016).

CONCLUSION

The study proves that *Aedes aegypti* in Southern Ghana are resistant to Deltamethrin but the level of resistance varied across the study sites. *Aedes aegypti* in Tema with a mortality rate of 57.8% were more resistant to deltamethrin than those in cape coast (80%) and Takoradi (86.6%). The mechanisms used by *Aedes aegypti* to resist the high toxicity of Deltamethrin must be investigated to establish its full resistance profile to make good vector control decisions. The world Health Organization (WHO) highlights the necessity of developing novel control methods that may contribute to the reduction of the mosquito populations and disease burden. Proposed innovative methods include the use of genetically modified mosquitoes, producing new traps or baits, and finding new insecticide and repellent molecules that are safe and environmentally friendly (WHO, 2017).

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