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Research Article

High Resistance to Deltamethrin and DDT in Major Malaria Vector *Anopheles gambiae s.l.* from South-Western Nigeria is Driven by Metabolic Resistance Mechanisms

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ABSTRACT
Insecticide resistance in *Anopheles gambiae s.l.* poses a significant challenge to malaria vector control efforts in Nigeria. Both target-site insensitivity and metabolic resistance have been implicated in the resistance process, with the latter often receiving less attention. To address this, we assessed metabolic enzyme activities in *Anopheles gambiae s.l* populations resistant to Deltamethrin and Diethyldichlorotriethylethane (DDT) in South-West Nigeria. A total of 600 *Anopheles* larvae were collected from all sites (Ibadan, Oyo, Badagry and Lagos) and resistance was classified according to WHO guidelines. Insecticide-exposed and unexposed cohorts were examined for metabolic enzyme activities. Results were compared between exposed and unexposed samples: ANOVA ($P<0.05$). Mosquitoes were identified as *An. gambiae* (89%, Ibadan; 0%, Badagry) and *An. coluzzii* (11%, Ibadan; 100%, Badagry). The population exhibited varied resistance levels: Deltamethrin mortality was 26% in Ibadan and 71% in Badagry while DDT mortality rates were 2% and 44% respectively. Biochemical analysis revealed significantly elevated levels ($P<0.05$) of cytochrome P450 and Gluthathione-S-Transferases in resistant vs susceptible samples. This finding underscores the need for integrated vector management strategies that specifically address metabolic resistance mechanisms in the country.

Keywords: *Anopheles coluzzii*; *Anopheles gambiae;* Cytochrome P450; Gluthathione-S-Transferases; Insecticide resistance

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INTRODUCTION

Malaria remains one of the deadliest parasitic diseases globally, affecting millions each year (Theoharides, 2015). The most vulnerable populations include children under five and pregnant women, whose immune responses are lower (WHO, 2019). In sub-Saharan Africa, Nigeria stands out as a significant contributor to global malaria cases and deaths (WHO, 2019), accounting for the highest burden worldwide, with an estimated 51 million cases and 207,000 deaths annually (Dawaki, 2016). The widespread presence of malaria is primarily attributed to the abundance of its main vector species, *Anopheles gambiae* s.l. and *Anopheles*

funestus s.l. (Oyewole and Awolola, 2006; Adesoye *et al*., 2024a, Adeogun *et al.,* 2023; Adeogun *et al.,* 2025).

To combat malaria, vector control efforts have focused heavily on the use of Long-Lasting Insecticide Nets (LLINs) and Indoor Residual Spraying (IRS). These strategies rely on insecticides from four main classes (Oduola *et al*., 2019) and are among the most effective tools for malaria prevention (Omotayo *et al*., 2021). The widespread adoption of LLINs and IRS in sub-Saharan Africa has reduced malaria incidence over the years (Omotayo *et al*., 2021). However, mosquito populations have developed resistance to all insecticides recommended by the WHO for malaria vector control, undermining many of the previous gains (Djouaka and Seun, 2016; WHO, 2021).

Some mosquito populations now exhibit resistance to two or more classes of insecticides approved for public health use (Oduola *et al*., 2012; Adeogun *et al*., 2017). Two primary resistance mechanisms have been identified: target site mutations and enhanced metabolic enzyme activity. Target-site mutations, commonly referred to as 'kdr' (knockdown resistance) mutations, are well-understood and are associated with reduced efficacy of pyrethroids and DDT (Nkya *et al*., 2013; Adesoye *et al*., 2023). These mutations diminish the insecticide's knockdown effect (Fagbohun *et al*., 2019). More recent evidence suggests that changes in metabolic enzyme activity play an increasingly important role in resistance (Riveron *et al*., 2014). Enhanced metabolic resistance involves increased detoxification or heightened enzymatic activity that reduces the effectiveness of insecticides (Hemingway *et al*., 2004; Corbel *et al*., 2007; Liu, 2015; Adesoye *et al*., 2023). The presence of multiple resistance mechanisms can also result in cross-resistance to various insecticides, posing a significant challenge to the success of vector control programs (Hien *et al*., 2017; Namountougou *et al*., 2019).

In Nigeria, research on insecticide resistance has mainly focused on target-site mutations, with less attention to metabolic resistance mechanisms (Awolola *et al*., 2005; Muhammad *et al*., 2021). Effective management of insecticide resistance requires a comprehensive understanding of both the extent and distribution of resistance, as well as the mechanisms by which local vector populations develop it (Djouaka *et al*., 2016). Ongoing, systematic monitoring of the types and spread of resistance mechanisms is essential. In line with this, our study investigated the metabolic resistance mechanisms in populations of *Anopheles gambiae* s.l. that are resistant to Deltamethrin and DDT in South-West Nigeria.

MATERIALS AND METHODS

Study Site

The sites used for this study New Garage situated in an urban community in Ibadan, Oyo state, (Latitude 7.331425, Longitude 3.858757) and Marina Road situated in a semiurban community in Badagry, Lagos State (Latitude 6.414167, Longitude 2.878056), South-West, Nigeria (Figure 1). Ibadan has a tropical wet and dry climate in Oyo State. Rainy season usually lasts between April to October while dry season is from November to March. The topography of the State is one of the gentle rolling lowland in the south, rising to a plateau 40 metres and above in the North. Thick forest in the South gives way to grassland interspersed with trees in the north. Agriculture is the main occupation as the climate in the State favors the cultivation of crops like maize, yam, cassava, millet, rice, plantains, cocoa, palm produce, cashew (Official website of the Oyo State Government, 2019. https://oyostate.gov.ng/about-oyo-state) with cultivated areas providing breeding sites for mosquitoes. On the other hand, Lagos has a Tropical wet and dry or savanna climate. The city's yearly temperature is 28.67 °C (83.61 °F) and it is -0.79% lower than Nigeria's averages. Lagos typically receives about 132.01 millimeters (5.2 inches) of precipitation and has 193.63 rainy days (53.05% of the time) annually. Natural and man-made sources provide breeding sites for mosquitoes in Lagos.

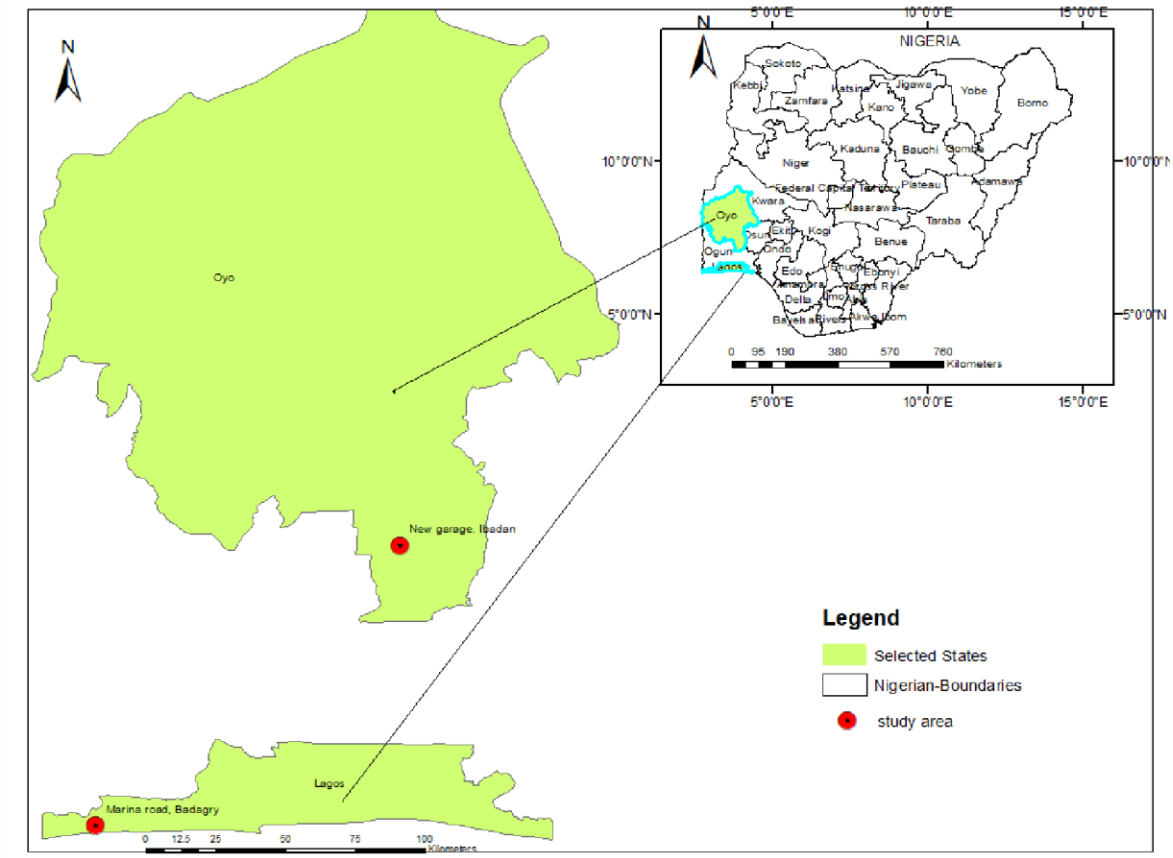

Figure 1. Study area where mosquito samples were collected

Mosquito collection and rearing

Anopheles larvae and pupae were collected from ditches and puddles using standard procedures (Service, 1971; Adesoye *et al.,* 2024b). They were then taken to the insectarium and transferred into larval bowls, suitably labelled and reared to adult at the insectary of Molecular Entomology and Vector Control Unit, Public Health and Epidemiology Division, Nigerian Institute of Medical Research, Yaba, Lagos, Nigeria (NIMR). Emerged adults were transferred to cages and provided with 10% sugar solution.

Insecticide susceptibility test

Susceptibility tests were carried out using WHO standard protocol (WHO, 2013) by exposing 25 female adult mosquitoes of 3-5 days old in 4 replicates to 0.05% Deltamethrin and 4% DDT impregnated papers. Controls using 25 mosquitoes in two replicates were also used. Mosquitoes knocked down were recorded at 10, 15, 20, 30, 40, 50 and 60minutes and mortality was determined after 24hours.

Determination of insecticide resistance mechanism using synergist

Cohorts of sampled populations were further exposed to synergist PBO and then Deltamethrin to detect resistant mechanisms according to WHO criteria (WHO, 2013). A total of 100 identified adult mosquitoes were first exposed to synergist PBO for one hour after which the samples were further exposed to Deltamethrin for another one hour. Mosquitoes knocked down were recorded at 10, 15, 20, 30, 40, 50 and 60minutes and mortality was determined after 24hours.

Morphological and PCR Identification of samples

Mosquitoes collected were identified morphologically using identification keys provided by Gillies and Coetzee, 1987. Molecular identification was done using PCR in line with the methods of (Scott *et al.,* 1993; Favia *et al.,* 1997).

Metabolic enzymes activity analysis

The microtitre plate method was used to determine enzyme levels in mosquito populations (WHO, 1998). Twenty-five (25) mosquitoes that survived exposure

to Deltamethrin and DDT insecticides were assayed for elevated esterase, cytochrome P450, glutathioneS-transferase (GST) and protein. Equal number of samples were analyzed from unexposed mosquitoes and the results compared between exposed and unexposed cohorts. All samples used for enzyme analysis were homogenized individually in 1.5ml eppendorff tubes containing 200µl of distilled water on ice. 25µl of homogenate per individual sample was kept in freezer at -200C. Esterase, cytochrome P450 and GST activities were determined and interpreted using standard procedures (WHO, 1998).

Data analysis

Mortality was determined after 24 hours and correction of percentage mortality with Abbott's formula was not necessary as mortality in all controls were below 5%. Resistance status was determined according to WHO criteria (WHO, 2013); mortality between 98100% indicates susceptibility, mortality between 90-97% suggests resistance, while mortality values below 90% indicates resistance. KDT50 and KDT95 values were determined using Probit regression analysis. Results (Mean ± Standard Error of Mean) for metabolic enzyme activities for exposed survivors and unexposed samples were compared using one-way analysis of variance with p-values set at 0.05. All statistical analysis were performed using SPSS version 23.0 (SPSS IBM Inc.).

RESULTS

Mosquito population used in the study

A total of 600 female *Anopheles* mosquitoes were used for the study. All mosquitoes were morphologically identified as members of *Anopheles gambiae* s.l. and further molecular analysis identified *Anopheles gambiae* (89% in Ibadan; 0% in Badagry) and *An. coluzzii* (11% in Ibadan; 100% in Badagry).

Susceptibility studies

Mosquito population from Ibadan was highly resistant to Deltamethrin with 24 hours mortality of 26%. Also, the mortality observed in DDT (2%) was extremely low (Table 1). Result of synergist assay showed increase in mortality values from 26% to 64% for Deltamethrin (Figure 2), however, the numbers of mosquitoes' knockdown after 60 mins of exposure to Deltamethrin (80%) and PBO+Deltamethrin (87%) were in close range.

Table 2 shows 24-hours post exposure mortality values of *Anopheles gambiae* s.l from Badagry, Lagos to Deltamethrin and DDT. Unlike the result obtained for population from Ibadan, mortality to DDT was 44% while mortality to Deltamethrin was 71%. When cohorts of same population were further exposed to PBO and deltamethrin, mortality to deltamethrin increased from 71% to 84% (Figure 3).

Table 1. Twenty-four hours post exposure mortality of *Anopheles gambiae s.l*. mosquitoes from Ibadan, Oyo exposed to diagnostic doses of Deltamethrin and DDT

Insecticide	No Exposed	KDT50 (min) 95% cl	KDT95 (min) 95% cl	Knockdown at 60mins	Mortality (%)	Susceptibility status
DDT (4%)	100	916.82	5582.96	2	2	Resistant
Deltamethrin (0.05%)	100	23.67 (21.07–26.35)	142.46 (108.09–10.68)	80	26	Resistant
PBO+Deltamethrin	100	27.76 (24.27–31.57)	77.09 (61.65–109.67)	87	64	Resistant

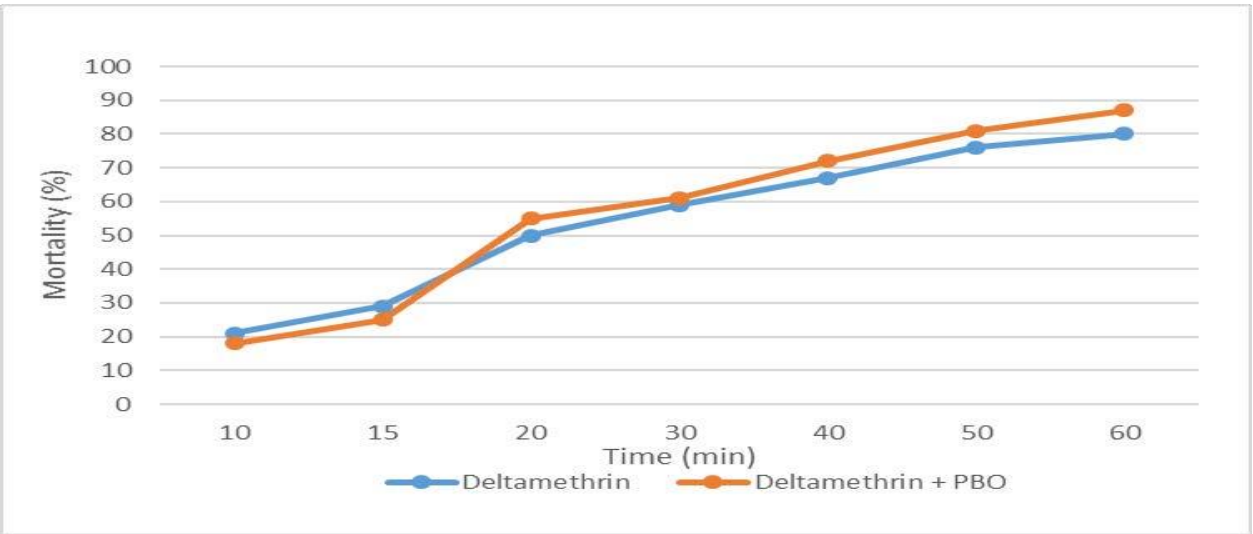

Figure 2. Percentage knockdown of *Anopheles gambiae s.l* from Ibadan, Oyo exposed to Deltamethrin only and Deltamethrin + PBO for 60 mins

Table 2. Twenty-four hours post exposure mortality of *Anopheles gambiae s.l.* mosquitoes from Badagry, Lagos exposed to diagnostic doses of Deltamethrin and DDT

Insecticide	No Exposed	KDT50 (min) 95% cl	KDT95 (min) 95% cl	Knockdown at 60mins	Mortality (%)	Susceptibility status
DDT (4%)	100	74.15 (64.08- 92.08)	257.66 (179.44-457.27)	36	44	Resistant
Deltamethrin (0.05%)	100	44.87 (41.84–48.56)	117.55 (99.32–147.54)	64	71	Resistant
PBO+Deltamethrin	100	37.30 (34.80–40.16)	104.83 (89.73–128.27)	78	84	Resistant

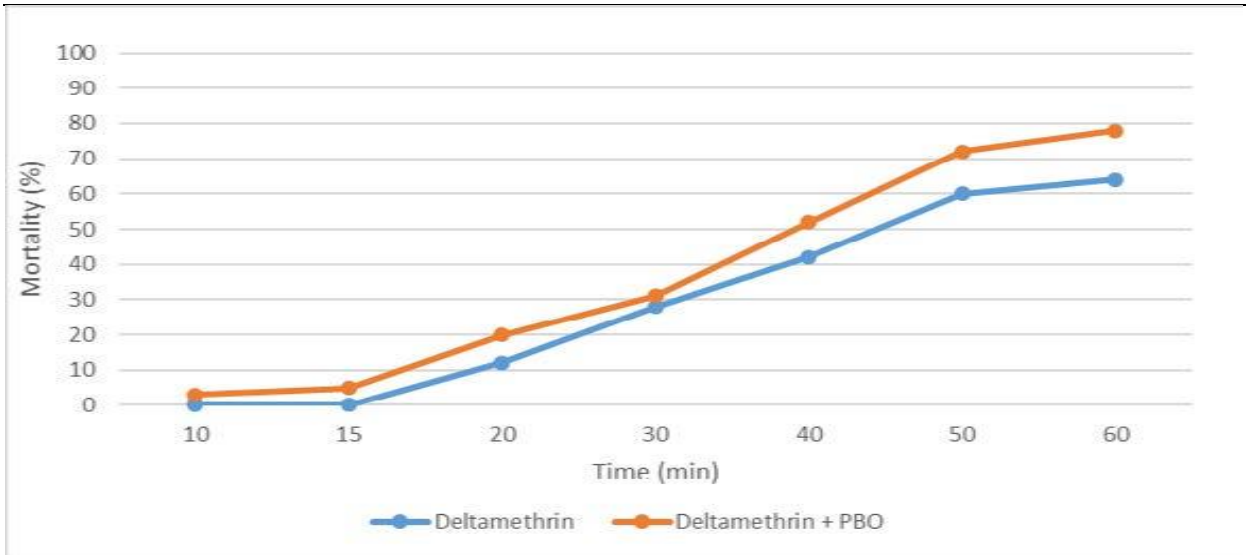

Figure 3. Percentage knockdown of *Anopheles gambiae s.l* from Badagry, Lagos exposed to Deltamethrin only and Deltamethrin + PBO for 60 mins

Metabolic enzymes activities

Result of metabolic enzymes assay is presented in Table 3. Esterase activities were slightly elevated ($p>0.05$), while that of cytochrome P450 and GST were significantly elevated ($p<0.05$) in DDT exposed samples from Ibadan as compared with unexposed samples. The same was observed in values for samples from Badagry when compared with unexposed samples. A similar trend was observed in samples exposed to deltamethrin; enzyme activities were generally elevated ($p<0.05$) in the exposed mosquitoes compared with the unexposed except for esterase.

Table 3. Mean values of enzyme activity in Anopheles gambiae s.l mosquitoes exposed to both Deltamethrin and DDT in South-West Nigeria

Location	Insecticide	Enzyme		
		Esterase	Cytochrome P450	GST
Ibadan, Oyo	DDT	1.81 ± 0.41^{a}	15.59 ± 3.87^{c}	51.72 ± 7.45^{d}
	Deltamethrin	3.00 ± 2.19^{a}	12.00 ± 1.94^{b}	30.05 ± 4.71^{c}
	Unexposed Samples	1.30 ± 0.40^{a}	5.51 ± 1.12^{a}	12.60 ± 2.05^{a}
Badagry, Lagos	DDT	0.24 ± 0.02^{a}	13.63 ± 1.89^{b}	48.09 ± 3.01^{d}
	Deltamethrin	1.27 ± 0.10^{a}	15.61 ± 2.41^{c}	49.15 ± 5.89^{d}
	Unexposed Samples	1.21 ± 0.61^{a}	4.73 ± 1.31^{a}	15.56 ± 3.35^{ab}

Note: Values are presented as mean ± standard error of mean. Values with the same superscript in a column connotes significant difference ($p<0.05$) and vice-versa.

DISCUSSION

The development of resistance in *Anopheles* populations in Nigeria is already alarming and it poses a serious threat to malaria vector control programs. Despite the huge number of LLINs distributed, data on annual malaria incidence remain unchanged (WHO, 2019; WHO 2021). Studies have shown that local populations of *Anopheles* are now resistant to all four classes of WHO-approved insecticides used for mosquito control in the country (Awolola *et al.,* 2007; Oduola *et al.,* 2012B). This highlights the need for proper resistance monitoring and characterization to inform policy decisions. Most reports in the country focus on the frequency of *kdr* resistance mechanisms with little to no efforts to properly implicate the resistance protein.

Mosquito populations in the present study were highly resistant to Deltamethrin and DDT which indicate cross-resistance within the populations (Riveron *et al.,* 2014; Adesoye *et al.,* 2023). This resistance data is consistent with previous reports from South-West Nigeria (Oduola *et al.,* 2012B). In many populations, cross-resistance has been largely attributed to the presence of kdr resistance gene (Chandre *et al.,* 1999; Dai *et al.,* 2015; Hancock *et al.,* 2018). Albeit, the frequency of kdr in the studied populations was not investigated, previous data suggest that kdr is one of the resistance mechanisms in populations of *Anopheles gambiae s.l*. from South-West Nigeria (Awolola *et al.,* 2007). Also, the high KDT50 values for both Deltamethrin and DDT in the study suggests high resistance intensity (Chandr et al., 1999; The PMI VectorLink Project. January 20190, which has been attributed to presence and high frequencies of kdr gene (The PMI VectorLink Project. January 2019).

Results from synergist assay where mortality was increased after pre-exposure to PBO suggest metabolic enzymes are also involved in resistance development. This result is also consistent with recent reports in South-West Nigeria that showed the involvement of cytochrome P450 in resistance process against pyrethroid based insecticides in malaria vectors (Fagbohun *et al.,* 2019; Adesoye *et al.,* 2024a). Also, evidence for this has been partly provided in a population of Anopheles in Nigeria where Permanet 3.0 (PBO + Deltamethrin) performed better than Permanet 2.0 in a phase III trial (Adeogun *et al.,* 2012).

Levels of cytochrome P450 was significantly higher in the Deltamethrin exposed samples from the two populations thereby suggesting its involvement in resistance development. Cytochrome P450 elevation had earlier been reported in different pyrethroid resistant populations in South-West Nigeria (Fagbohun *et al.,* 2019). A study by (Wanjala *et al.,* 2018) also reported cytochrome P450 elevation in Anopheles mosquitoes resistant to pyrehtroids and

DDT from some localities in Kenya. The impact of significant high level of cytochrome P450 in Anopheles population from South West Nigeria will be a strong disadvantage to the use of pyrethroid only net and this provide evidence for introduction of LLIN impregnated PBO and Pyrethroid as the introduction of PBO will increase the potency of pyrethroids as seen in the present study. Also, GST elevation was observed in DDT-resistant samples from both Ibadan and Badagry populations. This is similar to the work of (Perera et al., 2008) who reported elevated level of GST in DDT-resistant Anopheles population. In Nigeria, AlHassan *et al.* (2015) also reported significant GST elevation in DDT-resistant Anopheles population from North-West, Nigeria which is also consistent with data from other parts of Africa (Ibrahim *et al.,* 2016; Marcombe *et al.,* 2017; Simma *et al.,* 2019).

The essence of properly characterizing resistance mechanisms cannot be overemphasized. Due to the sustained levels of resistance to pyrethroids in Nigeria, the National Malaria Elimination Program (NMEP) is distributing Intersector G2 nets, which has insecticides with different resistance mechanisms to manage resistance. However, as in other studies, if multiple enzymes are involved in the resistance mechanisms in the country, the race to manage resistance might become more complicated. The obvious in this work is that, it appears pyrethroids resistance is mediated by elevated levels of cytochrome P450 with unusually high levels of Gluthathione S transferases. Such report is consistent with Adesoye *et al* (2024b) who discovered the same trend in laboratory KISUMU strains. As a result, more work needs to be done on characterizing metabolic enzymes across Nigeria for the NMEP to make informed decisions on resistance management in the country.

Furthermore, the geometric spread of insecticide resistance in all common vectors of malaria within the country calls for concern. Though, the NMEP aims to reduce malaria by investing more in vector control and reducing entomological innoculation rates to the barest minimum (NMSP, Nigeria 2014-2020), it may be hence, pertinent to invest more in vector surveillance and characterization of resistance mechanisms. This will guide in decision making as regards the rotation of insecticides or more essentially the introduction of integrated approach not including chemical larvicides in the country.

CONCLUSION

The resistance of *Anopheles gambiae* and *Anopheles coluzzii* to Deltamethrin and DDT insecticides in South-West, Nigeria is influenced by the elevation of Cytochrome P450 and Glutathione-S-Transferases. As such, the National program needs to prioritize the generation of widespread evidence on resistance mechanisms in the country, and make informed decisions on non-chemical vector control interventions.

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Conflicts of Interest

The authors declare no conflict of interest.

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