Patterns Of Insecticide Resistance Among Anopheles Gambiae Mosquitoes In Five Districts In Uganda: 2011-2015

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Abstract

Background: Malaria ranks among the leading global public health challenges. Resistance to insecticides used in vector control by malaria vectors threatens the effectiveness of this intervention. We analyzed data from routine susceptibility tests conducted in sentinel sites in five Ugandan districts to determine the status and pattern of insecticide resistance among *Anopheles gambiae* mosquito vectors, and to assess the trend of mortality rates of the vector.

Methods: We conducted a cross-sectional study using secondary data from sentinel sites in Apac, Kanungu, Hoima, Tororo, and Wakiso Districts of Uganda. Chemicals from different classes of insecticides were subjected to susceptibility tests, which included both the World Health Organization (WHO) standard test kit and the Centers for Disease Control and Prevention (CDC) bottle bioassay tests. Resistance was defined according to the standard WHO criteria of insecticide resistance. The Fisher's Exact Test was used to determine the difference in mortality rates across years in the study period.

Results: A total of eight chemicals were used in the selected districts over the years of study. Out of the 5 districts, we found that the average mortality rate of the mosquito vector by the carbamates was over 98% in 3 districts. In Tororo and Wakiso Districts, the average was about 90%. Mortality of mosquitoes by pyrethroids used averaged less than 80% in all five districts. The organochlorines averaged less than 50% in four out of five districts. In Apac District, organochlorines averaged a mortality rate of 94%. The organophosphates averaged 100% mortality in all sentinel sites. There was no specific pattern in mortality of *Anopheles gambiae* by insecticides.

Conclusion: There was widespread resistance to pyrethroids and organochlorines, with patchy resistance observed against carbamates. Only organophosphates showed potency in all sentinel sites. This threatens gains made in malaria control, and renews calls for continued insecticide resistance monitoring.

Background

Globally, malaria remains a leading cause of morbidity and mortality. It's estimated that 214 million malaria cases occurred in 2015, with approximately 440,000 deaths; an estimated 88% of these cases and 90% of deaths occur in sub-Saharan Africa (1). In recent years, the burden of disease due to malaria in sub-Saharan Africa has been on the decline (2). In Uganda, interventions to control malaria namely: integrated vector management, case management, and a strong surveillance and monitoring and evaluation mechanism saw a decline in incidence and mortality of the disease by over 40% between 2010 and 2015 (3). Despite the apparent success of these interventions, the burden of malaria in Uganda still remains high, with incidence rates at 19%, with relatively high mortality rates (4).

Over the last 15 years, countries in sub-Saharan Africa have intensified the use of vector control interventions for malaria control and prevention (5). The use of bed-nets and indoor residual spraying are the most widely employed interventions. This has resulted in tremendous success in reducing malaria-related morbidity and mortality figures. Between 2000 and 2015, malaria incidence reduced by 37% globally and 42% in Africa; in the same period malaria mortality rates reduced by 60% globally and 66% in Africa (6). These interventions, by nature of their application, involved the use of chemicals in reducing vector populations. The agricultural sector, especially livestock management, also uses chemicals with similar derivatives as those used in malaria vector control. The resultant effect is heightened selection pressure by malaria vectors to develop resistance to the widely used chemicals (7). Hence, progress that had been previously registered is now threatened by the emerging resistance to insecticides among Anopheline mosquitoes.

Since 2010, 60 countries have reported resistance among mosquitoes to at least one of the four dominant insecticide classes, with 49 of those reporting resistance to two or more classes (5). Pyrethroids are currently the only class of insecticides approved for use in bed nets (8); the other classes of chemicals used for malaria vector control are

carbamates, organochlorines, and organophosphates. According to the Global Plan for Insecticide Resistance Management (GPIRM) in malaria vectors, countries in sub-Saharan Africa and India are of the greatest concern because of a combination of widespread resistance and high transmission rates (5). Sampled strategies in the roadmap document include rotation of insecticides; combination of insecticide-based interventions; mosaic spraying and mixtures. However, the effectiveness of these strategies is dependent on a number of factors, which include the existence of updated data on country-specific insecticide resistance situation. The document reports limitations such as fragmented data with a narrow scope and depth, and databases tailored for research purposes, and not for prompt decision making. The absence of a clear mandate for the development of a database for the monitoring of insecticide resistance is yet another challenge (5).

In Uganda, all four classes of chemicals approved for use in malaria control interventions have been used. The National Malaria Control Program coordinates bi-annual studies on insecticide resistance, results of which are entered in the national malaria control program database.

We analyzed data from susceptibility tests conducted in sentinel sites in five Ugandan districts from 2011 to 2015 to determine the status and pattern of insecticide resistance among *Anopheles gambiae* mosquito vectors, and to assess the trend of mortality rates of the vector.

Methods

Study design and data source

This was a retrospective cross-sectional study. We performed a secondary analysis of insecticide susceptibility test data, from 2011 to 2015; obtained from the national insecticide resistance database. Data from insecticide susceptibility tests conducted in sentinel sites around the country are entered in an electronic database, which is managed by the Uganda National Malaria Control Program.

We selected five of the eleven sentinel sites for which there were analyzable data in the database in the period of interest. The sentinel sites were purposively selected to represent the region of the country they are located in and malaria transmission levels. Apac District in Northern Uganda and Tororo District in Eastern Uganda are high transmission areas, while Kanungu District in Southwestern and Wakiso District in Central Uganda are low transmission areas. Hoima District is situated in Western Uganda and is a medium transmission area **(Figure 1)**. We specifically looked at *Anopheles gambiae* mosquito species, which is dominant in Uganda.

Susceptibility tests

Insecticide susceptibility tests at the sentinel sites employed both the WHO standard test kit and the CDC bottle bioassays. The WHO susceptibility test measures mortality of mosquito species to discriminating concentrations, which are established under standardized laboratory conditions for all insecticides currently in use in malaria control programs (9). For the WHO susceptibility studies, mortality was recorded after 24 hours. In the CDC bottle bioassays, test mosquitoes are introduced into bottles coated with insecticide concentrations desired to be tested and mortality recorded every 15 minutes for 2 hours (10). Using the CDC bottle bioassay, the diagnostic time for most commonly used insecticides is 30 minutes, but its 45 minutes for DDT.

Data abstraction

Data on susceptibility tests using pyrethroid chemicals (i.e. permethrin 0.75%, deltamethrin 0.05%); organophosphates (i.e. pirimiphos methyl 0.25%, malathion 5.0% and fenitrothion 0.1%); carbamates (i.e. bendiocarb 0.1% and propoxur 0.1%); and organochlorine chemical (i.e. dichlorodiphenyltrichloroethane — DDT) were abstracted from the database. In the years considered for study, all four categories of insecticides approved for use by the World Health Organization

Pesticide Evaluation Scheme (WHOPES) were considered. Other data abstracted included the geographical location of assay, year the test was conducted, and vector mortality rates.

Statistical analysis

Test data were stratified by insecticide, class, location, year of assay, and proportion of mosquito mortality. Susceptibility status of mosquitoes to insecticides was evaluated according to the WHO criteria. Confirmed resistance is mortality at rates less than 90%; probable resistance is mortality rates between 90% and 97%; while susceptibility is mortality of at least 98% (9,10).

The Fisher's Exact Test was used to compare the differences in mortality between two successive years of data collection. The cut-off *p*-value was set at 0.05.

Map showing spatial location of sentinel sites was drawn using QGIS software (QGIS Development Team, 2009. QGIS Geographic Information System, Open Source Foundation Project. http://qgis.osgeo.org).

Ethical considerations

Ethical clearance for this study was obtained from the Uganda Ministry of Health and from the U.S. Centers for Disease Control and Prevention (CDC), where the evaluation was deemed non-research. Within the Ministry of Health, permission was also obtained from the National Malaria Control Program to access their data.

Results

Chemicals applied in the study districts, Uganda, 2011-2015

In Apac District, propoxur, pirimiphos-methyl, malathion and fenitrothion were applied in single years. Fenitrothion was only used in Apac District. In Tororo District, pirimiphos-methyl was also applied in a single year. In Kanungu District, malathion was not applied. In Wakiso District, propoxur , pirimiphos-methyl, and malathion were applied in single years. In Hoima District, DDT, deltamethrin, and pirimiphos-methyl were used in single years, while propoxur, permethrin and malathion were not used during the period of study **(Table 1)**.

Susceptibility status of *Anopheles gambiae* mosquito vectors against chemicals, Uganda, 2011-2015

Carbamates

In Apac District, *Anopheles gambiae* mosquitoes were fully susceptible to bendiocarb in all the years the chemical was used in the assays. Propoxur was used only in 2011, and the vector was susceptible. In Hoima District, there was a 4% drop in mortality of the mosquito vector by bendiocarb from 99% in 2011 to 95% in 2013, indicating a shift from susceptibility to partial resistance. In Kanungu District, mortality of *Anopheles gambiae* mosquitoes by bendiocarb was 97% signifying probable resistance. In 2013, mortality by bendiocarb increased by 3% signifying susceptibility. Mortality proportions remained the same in 2015. There was 100% mortality of vector by propoxur in Kanungu District in 2011, 2013 and 2015. In Tororo District, there was a 12% increase in vector mortality by bendiocarb and 17% mortality increase by propoxur. However, *Anopheles gambiae* vector mosquitoes were not susceptible to both chemicals in Tororo District. In Wakiso District, bendiocarb, which was potent against the Anopheline vector in 2011, dropped in mortality by 14% in 2013. The vector mosquitoes were not susceptible to bendiocarb in Wakiso in 2013. There was only probable resistance to propoxur in 2013, the year it was used in Wakiso District **(Figure 2)**.

Pyrethroids

In 2011 and 2013, there was confirmed resistance to both deltamethrin and permethrin in Apac and Hoima Districts. There were no data for tests conducted in both districts in 2015. In Kanungu District, there was confirmed resistance to deltamethrin in 2011 and 2015 and total resistance in 2013. The mosquito vectors were not susceptible to Permethrin in all the years in Kanungu District. In Tororo District, there was confirmed resistance to both deltamethrin and permethrin in all the years of testing. In Wakiso District, there was partial susceptibility to both permethrin and deltamethrin in 2011. However, there was a 53% drop in mortality by deltamethrin and 73% drop by permethrin in 2013, therefore signifying full resistance **(Figure 2)**.

Organophosphates

The mosquito vector was susceptible to all organophosphates in all the sentinel sites in all the years they were used for testing **(Figure 2)**. Chemicals in this class were applied in Apac and Hoima Districts only in 2011.

Organochlorines

In this category, only one chemical (DDT) was applied. Except in Hoima District where it was applied only in 2013, in the rest of the districts, it was applied in 2011 and 2013. In all the districts, the chemical did not show any potency against malaria vector. In Apac District, the chemical was a partial susceptibility of *Anopheles gambiae* to DDT. In all the other sentinel sites, there was full resistance with mortality **(Figure 2)**.

Trends of *Anopheles gambiae* mortality, Uganda, 2011-2015

In Apac District, there was a 59 percentage point increase in mortality by deltamethrin between 2011 and 2013, and 54%-point increase by permethrin in the same period. Both increases were significant ($p<0.01$). In Kanungu District, there was a 45% drop in the mortality of *Anopheles gambiae* malaria vector between 2011 and 2013 by deltamethrin and a similar rise during 2013 to 2015. Within the same periods, the district registered a 54% and 26% drop in permethrin mortality respectively. However, the drop between 2013 and 2015 was not significant ($p=0.26$). In Tororo District, there were drops in malaria vector mortality by both deltamethrin and permethrin. While the 44% decline by deltamethrin was significant ($p=0.0001$), permethrin did not register a significant decline ($p=0.32$). Wakiso District registered significant declines in malaria vector mortalities by both deltamethrin and permethrin ($p<0.01$). Deltamethrin mortality declined by 54%, while permethrin mortality dropped by 73%.

Organophosphate chemicals did not show any significant difference in mortality of malaria vectors in all selected districts over the years of study ($p=1.0$).

Mortality of malaria vectors by DDT improved in Apac District between 2011 and 2013. However, this was not significant ($p=0.57$). In Kanungu District, there was a 64% improvement in mortality of malaria vector by DDT from 2011 to 2013; this increase was significant ($p=0.002$). In Wakiso District, the 54% decline in mortality by DDT was significant ($p=0.02$), while that in Tororo District was not significant ($p=0.36$).

The carbamate chemicals did not show any significant trend in Apac, Hoima and Kanungu Districts across the years of application. In Tororo District, there was a 12% increase in mortality of *Anopheles gambiae* mosquitoes by bendiocarb and propoxur between 2011 and 2013. In Wakiso District, there was a 14% decline in mortality by bendiocarb between 2011 and 2013. The changes in both Tororo and Wakiso Districts were significant (**Table 2)**.

Discussion

Organophosphate chemicals were the only potent chemicals against *Anopheles gambiae* mosquito vectors in all five districts in the years of study. Organophosphates registered average mortality rates of 100% across the five sentinel sites selected for the study. There was relative resistance to carbamate chemicals in Tororo and Wakiso Districts. In Hoima

District, there was a decline in potency of bendiocarb, a carbamate. There was widespread resistance by *Anopheles gambiae* to both organochlorines and pyrethroids in all districts selected for the study. There has been a scale-up of vector control methods in sub-Saharan Africa in the last decade (11). This may have led to a prolonged exposure to insecticides, which is likely to have led to selection of insecticide resistance among mosquito vectors (12).

Results from our study showed varied mortality rates of mosquito vectors by pyrethroid chemicals in all districts selected; however in none of the sites was full susceptibility demonstrated. *Anopheles gambiae* mosquitoes did not show any susceptibility to DDT in any of the sites selected. Over the study period, emergence of probable resistance to bendiocarb was seen in Hoima and Tororo Districts. Our findings are similar to studies conducted in Kenya, which found resistance of *Anopheles gambiae* mosquitoes to pyrethroids and DDT and patchy resistance to bendiocarb (11). Koekemoer *et al.* in their 2011 study in Congo also reported widespread resistance by *Anopheles gambiae* mosquito species to DDT and pyrethroid chemicals, deltamethrin and permethrin (13). In most sub-Saharan countries, Uganda inclusive, insecticide treated mosquito nets (ITNs) and indoor residual spraying are the most widely used vector control strategies (12). Currently, pyrethroids are the only WHO-approved class of chemicals used in bed-nets (5). Resistance to this class of insecticides, therefore, negatively impacts on this vector control intervention. This worrying resistance trend of resistance by malaria vectors may have been caused by the continued exposure of these chemicals to mosquitoes. Besides use in ITNs, vectors become exposed to chemicals used in agriculture by contamination of breeding sites (14). Many insecticides used in agriculture have similar derivatives as those used in malaria vector control (15).

For continued effectiveness of ITNs, creative, yet evidence-based solutions have to be sought to counter this resistance. The use of the synthetic synergist, piperonyl butoxide (PBO) when used in combination with pyrethroids has been demonstrated to enhance susceptibility of *Anopheles gambiae* mosquitoes in Ghana (16). It has been suggested that for management of resistance, ITNs with PBO can revive the strength of pyrethroids against resistance malaria vectors (17).

Indoor Residual Spraying (IRS) in Uganda has in the very recent been conducted in twenty-five districts in Northern and Eastern Uganda. Indoor Residual Spraying has been used to great effect in reducing malaria incidence in areas where it has been applied (18, 19). DDT was last used in the country in a pilot in Northern Uganda before 2009, and has never been used for large scale IRS (18). The patchy resistance to bendiocarb as has been demonstrated by studies in these sentinel sites threaten these gains, as it is one of chemicals used in IRS, besides pirimiphos-methyl, an organophosphate (President's Malaria Initiative, Malaria Operational Plan, 2017). Resistance to carbamates, bendiocarb and propoxur, fenitrothion, an organophosphate have been demonstrated in Benin (20). The spread of this resistance to malaria endemic countries threaten all gains that have been achieved in malaria control. This underscores the need for insecticide resistance monitoring and appropriate response mechanisms need to be established in order to effectively control malaria.

Though our study did not attempt to establish an association between insecticide resistance and malaria incidence, a study in South Africa found an increase in malaria incidence fueled by resistance to pyrethroids and sulfadoxine-pyrimethamine A study in Kenya did not find any significant association between insecticide resistance and increased malaria incidence (21). However, this result is to be interpreted with caution as it may well be as a result of mechanical, rather than biological reasons. The consistent use of mosquito nets in good condition may provide a physical barrier to minimize mosquito bites and therefore transmission (22). However, it has been found that though resistance may be observed, vectors may still be susceptible to toxic doses of chemicals used on the nets; though they do not necessarily get knocked down (21).

Our study had limitations which may have affected the results of our study; first was missing data from the database. The erratic manner in which insecticides were applied in sentinel sites resulted in limited data to explore trends of mortality. Another limitation was that the WHO tube assay, which was also used in susceptibility tests is not very informative of the intensity of insecticide (21).

Conclusion And Recommendations

Insecticide resistance by one of the most dominant malaria vectors in the country threatens to reverse gains so far registered in malaria control in Uganda. The effectiveness of ITNs impregnated with pyrethroids stands to be questioned as these mosquito nets are reduced to mechanical barriers which reduce mosquito-man interface. The possibility of the spread of resistance of Anopheline mosquito vectors to carbamates and organophosphate insecticides provides the need to intensify vector monitoring. Strategies developed around the GPIRM may be helpful in appropriately managing this threat.

List Of Abbreviations

WHO: World Health Organization, CDC: US Centers for Disease Control and Prevention, DDT: Dichloro diphenyl trichlorethane, GPIRM: Global Plan for Insecticide Resistance Management, WHOPES: World Health Organization Pesticide Evaluation Scheme, PBO: Piperonyl butoxide, ITNs: Insecticide treated mosquito nets, IRS: Indoor Residual Spray.

Declarations

Ethical considerations

We utilized secondary data from routinely collected data at sentinel sites. We obtained permission to utilize the data from the Uganda Ministry of Health. Additionally, the U.S. Centers for Disease Control and Prevention (CDC) evaluated the study protocol and deemed it non-research.

Consent for publication

Not applicable

Availability of data and material

The data that support the findings of this investigation are available from the Uganda Ministry of Health and may be available from the corresponding author upon reasonable request and with permission of the ministry.

Competing interests

The authors declare that they have no competing interests.

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The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the funding agencies or Makerere University School of Public Health, and the Ministry of Health of Uganda.

Authors’ contributions

DO conceptualized the investigation idea and took lead in execution of the investigation. He wrote the drafts of the manuscript and revised the paper for substantial intellectual content. DR, DK, BK, ARA, and JO participated in the

conceptual design, development of the study and supervision. They also reviewed the manuscript for substantial intellectual content. DB, CB reviewed the paper for substantial intellectual content and were also involved in data analysis. All authors have read and approved the final manuscript.

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Tables

Table 1
Insecticide chemicals used in susceptibility tests in the selected sentinel sites, Uganda, 2011–2015

Chemical	Class	Location				
		Apac	Tororo	Kanungu	Wakiso	Hoima
Bendiocarb 0.1%	Carbamate	2011 2013 2015	2011 2013	2011 2013 2015	2011 2013	2011 2013
Propoxur 0.1%	Carbamate	2011	2011 2013	2011 2013 2015	2013	
DDT 4.0%	Organochlorine	2011 2013	2011 2013	2011 2013	2011 2013	2013
Permethrin 0.75%	Pyrethroid	2011 2013	2011 2013	2011 2013 2015	2011 2013	
Deltamethrin 0.05%	Pyrethroid	2011 2013	2011 2013	2011 2013 2015	2011 2013	2013
Pirimiphos-methyl 0.25%	Organophosphate	2011	2011	2011 2015	2011	2011
Malathion 5.0%	Organophosphate	2011	2011 2013		2013	
Fenitrothion 0.1%	Organophosphate	2011				

Table 2

†: Difference in mortality of *Anopheles gambiae* mosquito vector by chemical, Uganda, 2011–2015

Chemical	Period	p-values				
		Apac	Kanungu	Tororo	Hoima	Wakiso
Bendiocarb	2011 vs 2013	1.0000	0.1212	0.0015	0.0594	0.0003
	2013 vs 2015	1.0000	1.0000			
	2011 vs 2015	1.0000				
Propoxur	2011 vs 2013		1.0000	0.0039		
	2013 vs 2015		1.0000			
DDT	2011 vs 2013	0.5679	0.0018	0.35933		0.0212
Deltamethrin	2011 vs 2013	0.0000	0.0000	0.0001	1.0000	0.0001
	2013 vs 2015		0.0074			
Permethrin	2011 vs 2013	0.0000	0.0000	0.3221		0.0001
	2013 vs 2015		0.2649			
Pirimiphos-methyl	2011 vs 2015	1.0000	1.0000	1.0000	1.0000	1.0000
Malathion	2011 vs 2013			1.0000		

†Blank cells indicate the lack of a comparator, or that the chemical was not used in the sentinel site in the district.

Figures

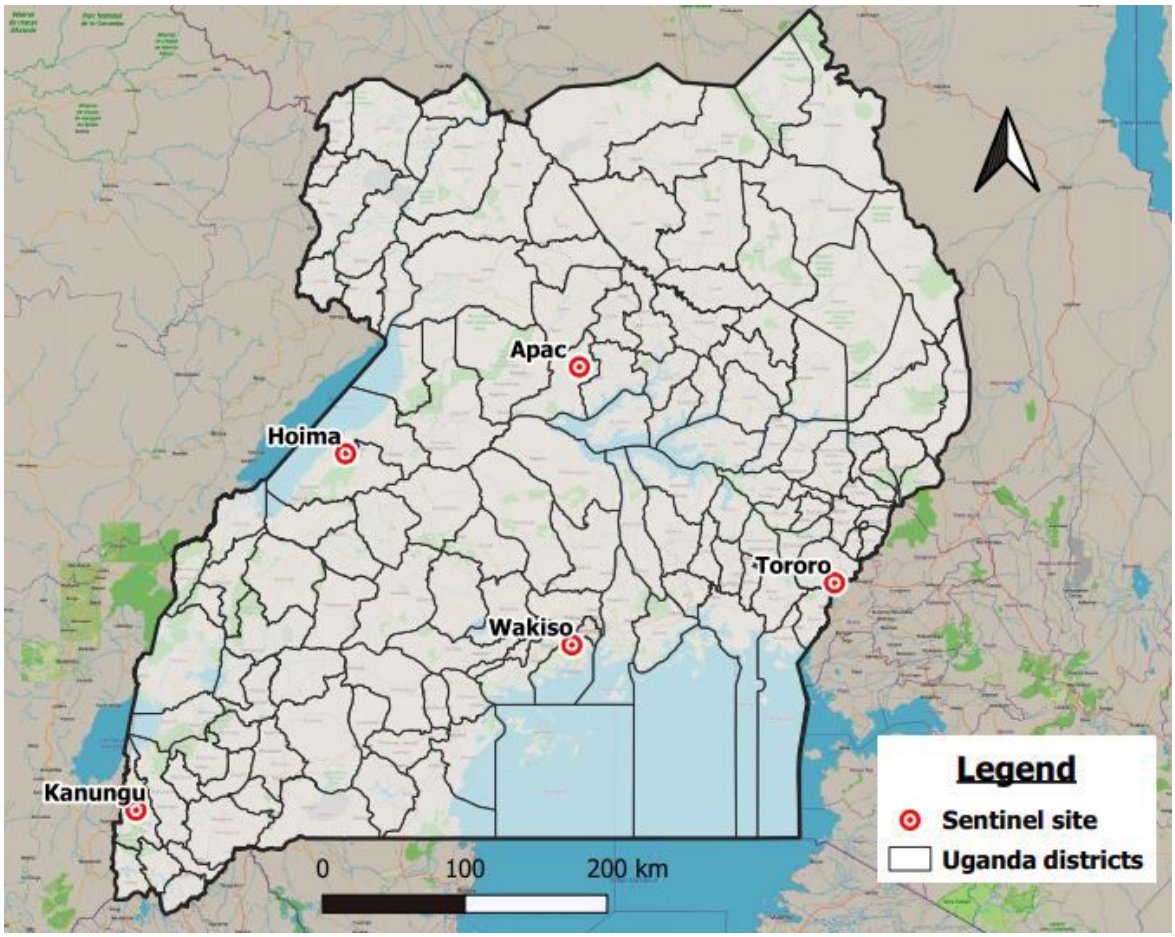

Figure 1

Location of the selected sentinel sites in Uganda

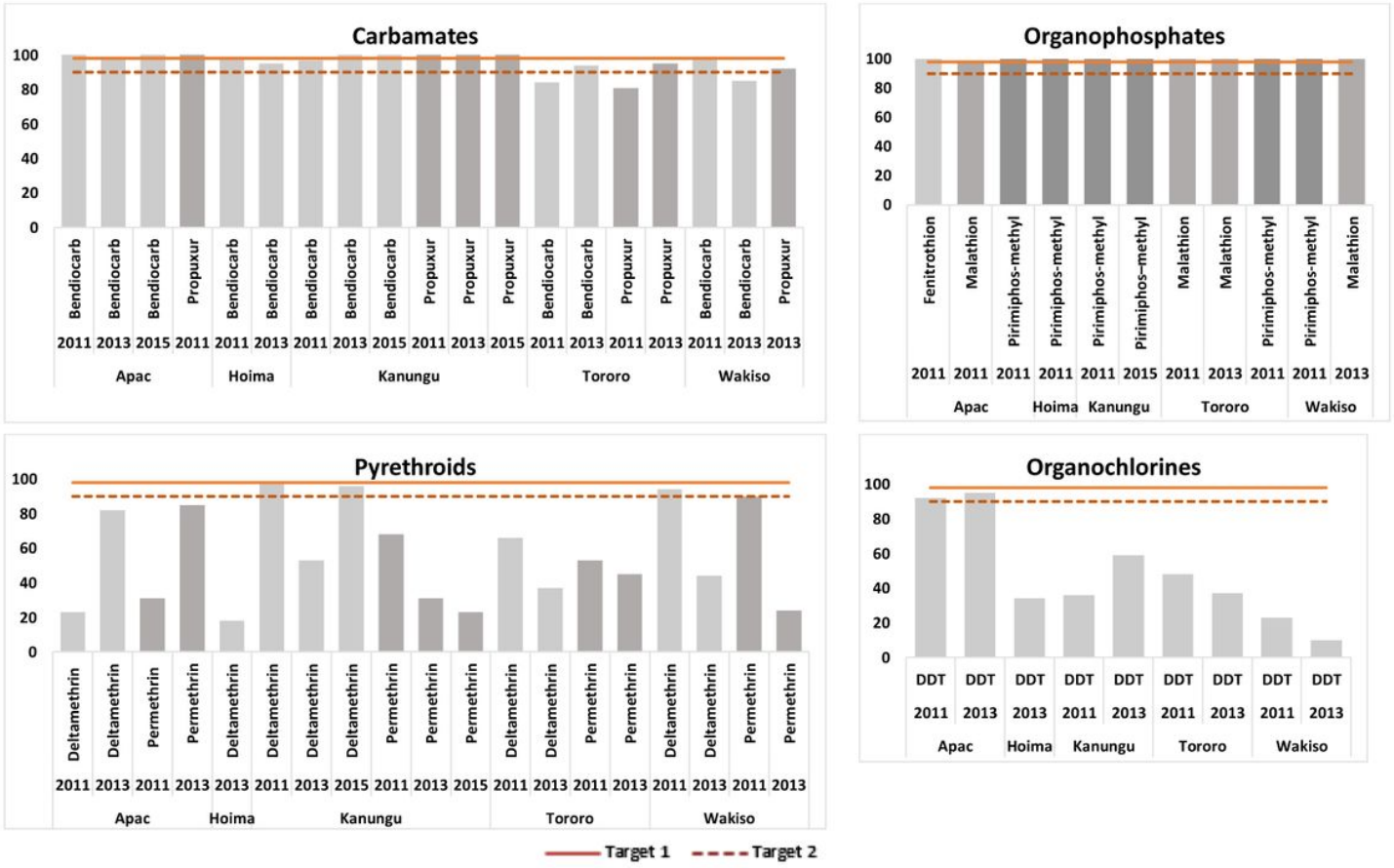

Figure 2

Mortality of Anopheles gambiae mosquito vector by insecticide chemical classes by district, Uganda, 2011-2015. The solid line on each figure represents the cut-off for susceptibility according to the WHO criteria (98%). The dotted line represents the cut-off for partial susceptibility (90%).