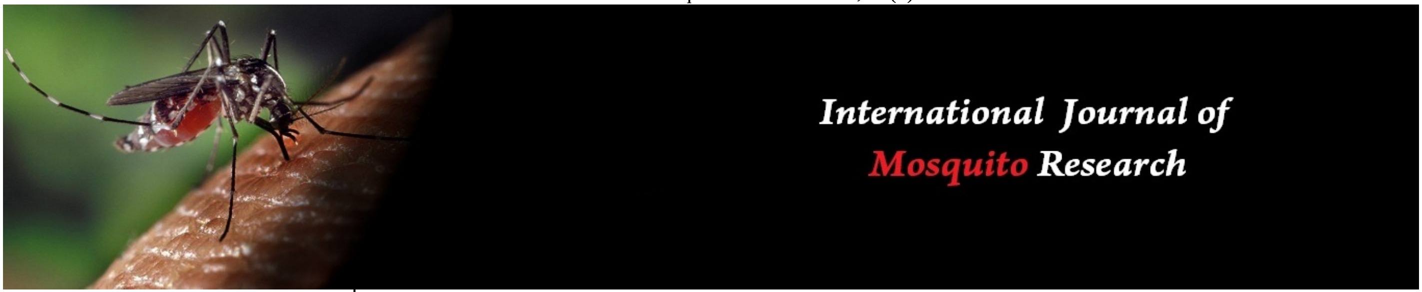

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Residual efficacy of fludora® fusion WP-SB 56.25 (A mixture of clothianidin and deltamethrin) against anopheles, culex, and aedes mosquitoes in tesseney district, western eritrea: A cross-sectional study

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Abstract
Introduction: In Eritrea, malaria remains a major vector-borne disease of significant public health concern. The disease exhibits high seasonality, focal distribution, and instability. Insecticides such as bendiocarb, pirimiphos-methyl, and a mixture of deltamethrin and clothianidin have been widely used for indoor residual spraying (IRS), with rotations occurring every two years based on the resistance status of local vectors. The objective of this study was to assess the residual efficacy of Fludora® Fusion WP-SB 56.25 (a mixture of clothianidin and deltamethrin).
Methods: Larvae of Anopheles, Culex, and Aedes mosquitoes were collected from both natural and artificial breeding habitats in the Tesseney district. The collected larvae were reared in the laboratory until they reached adulthood. Four-day-old female mosquitoes were used for cone tests following the WHO protocol. Cone tests were conducted on both cement and mud walls, with ten structures evaluated for each mosquito species. The residual activity of Fludora® Fusion WP-SB 56.25 (clothianidin + deltamethrin) against the different mosquito species was assessed at intervals of two, six, and twelve weeks post-IRS.
Results: Immediately following the spraying campaign, the residual efficacy of the insecticide exceeded the WHO's 80% threshold. However, its efficacy dropped below 80% over a period of three months. A slightly higher efficacy was observed on cement walls compared to mud walls. The residual efficacy of Fludora® Fusion was more pronounced against Anopheles and Aedes mosquitoes than against Culex mosquitoes.
Conclusion: The new formulation of Fludora® Fusion demonstrated residual efficacy lasting up to three months, suggesting that a second round of IRS may be advisable in areas with long transmission periods.

Keywords: Malaria, IRS, insecticides, Eritrea.

Introduction
Vector-borne diseases represent a major global health threat, imposing significant economic burdens on affected regions. Controlling the vectors responsible for transmitting disease-causing pathogens offers an effective means of preventing many of the most serious vector-borne diseases, including malaria [1]. As a result, vector control has become an essential part of strategies aimed at preventing, controlling, and eliminating malaria, due to its proven ability to provide personal protection and reduce transmission and disease burden [2]. The ideal approach is to ensure universal coverage for all populations at risk, particularly in various eco-epidemiological and endemic settings, using key interventions such as long-lasting insecticidal nets (LLINs) or indoor residual spraying (IRS).
Although there has been a notable reduction in malaria morbidity and mortality in recent years, it remains one of the leading public health challenges in sub-Saharan Africa [3, 4]. The scaling-up of insecticide-based strategies, including LLINs and IRS, continues to be recognized as an

effective method for preventing malaria transmission. Despite the benefits of IRS, significant variability in the duration of its efficacy has been observed, which depends largely on the specific insecticides used [5-7]. The widespread development of resistance to pyrethroids in many malaria-endemic regions of Africa, coupled with emerging resistance to carbamates, is a major concern. Therefore, ensuring the sustainability of IRS as a vector control method remains a critical challenge. One proposed solution to combat rapid resistance development is the rotational use of different insecticides [8]. However, due to the limited availability of alternative insecticides and the occurrence of cross-resistance between some classes, maintaining the residual efficacy of existing IRS tools requires the development of new and innovative insecticide formulations. The WHO recommends the rotational use of insecticides from various classes with different modes of action for IRS and encourages the development of mixtures or combinations to manage resistance. However, before widespread adoption of such insecticide combinations, it is essential to evaluate their residual efficacy and persistence on treated surfaces.

Fludora® Fusion, a combination of clothianidin (a neonicotinoid) and deltamethrin (a pyrethroid), developed by Bayer Crop Science, has been proposed for IRS. Clothianidin targets nicotinic acetylcholine receptors in the central nervous system of insects, causing overstimulation that leads to paralysis and ultimately, insect death [9]. In contrast, pyrethroids like deltamethrin work by interacting with voltage-gated sodium channels in insect neurons, causing neurotoxicity. The inclusion of clothianidin-based formulations in malaria vector control programs is particularly promising in areas with high levels of resistance to multiple insecticide classes [10, 11]. The greatest benefits are achieved when the targeted mosquito population is fully susceptible to the insecticide mixture's components [12].

IRS and LLINs have proven effective when properly implemented [13], and the scaling-up of these strategies has led to substantial reductions in malaria-related morbidity and mortality between 2000 and 2015 [14]. Indeed, Millennium Development Goal 6, which aimed to reverse the incidence of malaria by 2015, was successfully achieved [15]. However, since 2015, progress in malaria control has stagnated [16], largely due to the increasing resistance of malaria vectors to insecticides [17]. Insecticide resistance can significantly undermine the effectiveness of vector control strategies [18, 19]. From 2010 to 2020, 89% of countries that reported data globally observed resistance to at least one insecticide class in malaria vectors, with 33% detecting resistance to pyrethroids, carbamates, organophosphates, and organochlorines across multiple sites. Additionally, 22% of these countries reported resistance to all four insecticide classes in at least one site and one local vector species [20]. IRS is widely used to reduce human-mosquito contact and control malaria outbreaks. In Eritrea, IRS has been conducted in the Northern Red Sea (NRS) region until 2000, and since 1998, insecticides such as DDT, lambdacyhalothrin, and malathion were used routinely in the Gash Barka and Debub regions. DDT was the primary insecticide for IRS until 2011, when the country shifted to a rotation of carbamates and pyrethroids starting in 2012. From 2008 to 2021, three insecticides-pyrethroids, bendiocarb, and pirimiphos-methyl 300 CS-were used in rotation every two years on the walls. Currently, IRS is implemented in selected high malaria-endemic areas in the three zones (NRS, Gash Barka, Debub) using a new, cost-effective IRS product: a mixture of clothianidin 500 g/kg and deltamethrin 62.5 g/kg (neonicotinoid + pyrethroid). Clothianidin, a new insecticide in the neonicotinoid class, has been included on the WHO prequalification list for IRS use [21] after demonstrating effective performance against resistant vector populations in laboratory and semi-natural environments [22, 23] as well as in small-scale community trials [24, 25]. New-generation clothianidin-based insecticides offer longer residual activity in both community settings and large-scale applications compared to traditional neurotoxic insecticides.

This study was conducted to assess the residual efficacy of Fludora® Fusion (clothianidin 500 g/kg+ deltamethrin 62.5 g/kg) against Anopheles, Culex, and Aedes mosquitoes on cement and mud walls used in large-scale IRS operations implemented in Eritrea in 2022.

Materials and Methods

Study Site

The study was conducted in Shieb village, located in the Tesseney district, where the entomology laboratory center is based. This village is centrally located in the western part of the Gash Barka zone, with an estimated population of 7,000 people primarily engaged in farming and animal husbandry. The high movement of people in the area increases the risk of malaria importation, as well as the transmission of other vector-borne diseases and new mosquito species. The village is situated along the Gash River, providing permanent and diverse mosquito breeding sites. Shieb village lies at latitude 15°06'53" N and longitude 36°39'46" E, at an elevation of 610 meters above sea level (GPS coordinates). The entire breeding site is treated with Temophos and Bti to control larval populations, while pyrethroids are used for LLINs. For IRS, organophosphates, carbamates, and the newly introduced combined insecticide of Clothianidin and Deltamethrin are used in rotation every two years to prevent resistance development across the district.

IRS Campaigns

IRS campaigns are carried out annually in the Tesseney district using different classes of insecticides. In 2022, a mixture of Clothianidin (500 g/kg) and Deltamethrin (62.5 g/kg) was used. A total of 24,281 structures were sprayed throughout the district, aiming to protect a population of 75,433. Shieb village, one of the areas covered in the campaign, had 2,343 structures sprayed, protecting 7,000 inhabitants in 2022 [IRS REPORT 2022].

Insecticide Formulations Used

The insecticide formulation used was a wettable powder (WP) containing Clothianidin (500 g/kg) and Deltamethrin (62.5 g/kg), packaged in 100 g sachets that can be diluted for indoor residual spraying. The recommended application rate by the World Health Organization (WHO) is 0.4 g of product/m², corresponding to 200 mg/m² of Clothianidin and 25 mg/m² of Deltamethrin [26]. Clothianidin, a neonicotinoid, acts on the central nervous system of insects by binding to nicotinic acetylcholine receptors, leading to paralysis and death. Deltamethrin, a pyrethroid, blocks voltage-gated sodium channels in insect neurons, causing neurotoxicity.

Selection of Houses and Description of Key Activities

Tesseney district consists of eleven villages with similar geographical and climatic conditions. IRS with the combination of Clothianidin and Deltamethrin was carried out in all these villages in 2022. To assess the residual efficacy of this insecticide mixture, Shieb village was randomly selected. This village served as a representative site for evaluating the insecticide's performance on different types of walls, targeting various mosquito species present in the area.

Measured Parameters

The study evaluated three key parameters: one-hour knockdown effect, twelve-hour mortality, and twenty-four-hour mortality, for three mosquito species: Anopheles, Culex, and Aedes [27].

Mosquito Rearing

Mosquito larvae were collected from the locality of Selam (15°06.261' N, 36°39.865' W), a village in Tesseney district, between August and November 2022. All mosquito species (Anopheles, Culex, and Aedes) were reared in the laboratory under standard conditions (27 ± 2°C, 75% ± 5% relative humidity, and a 12-hour light/dark cycle). The immature stages of the mosquitoes were transported in larval containers and temporarily kept in larval trays. Once the mosquitoes emerged, they were fed sugar.

Selection of Test Specimens

The age, physiological condition, and gender of mosquitoes are important factors influencing study outcomes. Males were excluded from the study because they are generally smaller, have shorter life spans, and are more fragile than females, resulting in higher control mortalities. Only female mosquitoes aged four days that were sugar-fed (non-blood fed) were used in the study. Three species of mosquitoes (Anopheles, Culex, and Aedes) aged four days were exposed to fixed cones for 30 minutes [29, 30].

Inclusion and Exclusion Criteria

Inclusion criteria: Female Anopheles, Aedes, and Culex mosquitoes aged four days.

Exclusion criteria: Male mosquitoes, unhealthy mosquitoes, mosquitoes younger than two days or older than four days, and blood-fed mosquitoes were excluded from the study.

Sample Size

The sample size was determined according to the WHO cone bioassay test procedure. For the residual efficacy assessment, ten unit structures or households were randomly selected. In each structure, 27-30 adult female mosquitoes from each mosquito species (Anopheles, Culex, and Aedes) were exposed to the sprayed walls. Additionally, 8-10 mosquitoes of each species were used as controls to compare with the results from the exposed mosquitoes.

Bioassay

The bioassays were conducted in three rounds: one week, one month, and three months after spraying, following the WHO protocol [29, 30]. Ten unit structures were randomly selected, with five having cement walls and the other five having mud walls for the exposure tests. In each structure, three cones were placed at the top, middle, and bottom of the walls as treatment cones, and one cone was fixed with plain printing paper as a control. Ten non-blood fed female mosquitoes were placed in each cone and exposed for 30 minutes. After exposure, mosquitoes were aspirated into paper cups with netting and provided with a cotton bud soaked in 10% sucrose solution for feeding. The knockdown rate was recorded one hour post-exposure for each mosquito species. The mosquitoes were then transported to the entomology laboratory and kept for 24 hours at 27 ± 2°C and 73% ± 4% relative humidity. Mortality rates were recorded 12 and 24 hours after exposure.

Data Analysis and Interpretation

Data was entered into an Excel sheet and analyzed using SPSS (Version 25). Efficacy was assessed according to the WHO criteria, with mortality rates compared to the 80% efficacy threshold [28]. The mortality rate for each mosquito species was calculated as the number of dead mosquitoes divided by the total number of exposed mosquitoes, multiplied by 100. If the control mortality rate was between 5% and 20%, Abbott's formula was used to correct for control mortality. The corrected mortality was calculated using the following formula:

\text{% Corrected Mortality} = \frac{(\text{% Kill in Treated} - \text{% Kill in Control}) \times 100}{100 - \text{% Kill in Control}}

If control mortality exceeded 20%, the test was repeated. If the mortality rate was below 5%, the test was considered valid without the need for correction.

Results

A total of 801 *Anopheles gambiae*, 835 Culex, and 861 Aedes mosquitoes aged four days were exposed to the treated walls (both cement and mud). An additional 834 mosquitoes of all species served as controls. The knockdown and mortality rates of each mosquito species at different time points on various wall types were evaluated. The efficacy of Fludora® Fusion WP-SB 56.25 (a mixture of Clothianidin and Deltamethrin) insecticide showed a significant association between the three mosquito species (Anopheles, Culex, and Aedes) ($p < 0.001$) across the different time points. However, the mortality rates observed for Fludora® Fusion did not reach the WHO efficacy threshold of 80% for any of the mosquito species throughout the study period. Aedes mosquitoes exhibited higher immediate and delayed mortality rates compared to Anopheles and Culex mosquitoes after exposure to the treated walls.

Discussion

This study conducted a large-scale community evaluation of the efficacy of Fludora® Fusion (Clothianidin + Deltametrine) formulations used in Indoor Residual Spraying (IRS). The tested product was a mixture of neonicotinoids and pyrethroids (Clothianidin 500 g/kg + Deltametrine 62.5 g/kg). Clothianidin-based insecticides are emerging as potential alternatives to carbamates and organophosphates, to which resistance is increasingly observed.

Throughout the study, cone tests were conducted, and the residual efficacy of the treatments was assessed two weeks post-spraying. The results demonstrated that Fludora® Fusion (a mixture of Deltametrine and Clothianidin) was effective on both cement and mud surfaces. However, our findings indicated that Fludora® Fusion showed low residual efficacy on both substrates, with mortalities below the WHO efficacy threshold after three months. Similar results were reported by Fongnikin et al. [31], who observed prolonged high mortality of pyrethroid-resistant malaria vectors for 7-10 months using Fludora® Fusion. In contrast, our study showed residual efficacy at one month after exposure, but the formulation failed to achieve effective mortality at three months.

Table 1: Mean mortality rates at different time points for the tested insecticide formulations over the whole study period (combined data for both cement and mud walls). (Clot + Delt) = mixture of Clothianidin 500 g/kg and Deltametrine 62.5 g/kg; hr = hour; % = percentage: wks=weeks: IRS= indoor residual spraying

	WKS post IRS	Mortality rate			Chi-square test
		Anopheles	Aedes	Culex	
1hr knockdown	2wks post IRS	53.70%	80.30%	6.40%	<0.001
	6wks post-IRS	27.30%	59%	5.30%	
	12 wks post-IRS	23.30%	44.30%	3.70%	
12 hr mortality	2wks post IRS	69%	95%	16%	<0.001
	6wks post-IRS	70.70%	74.70%	16.30%	
	12 wks post-IRS	43.30%	47.30%	10%	
24 hr mortality	2wks post IRS	80%	98.30%	35.30%	<0.001
	6wks post-IRS	76.70%	81.70%	27.30%	
	12 wks post-IRS	52%	58.70%	16.3	

Table 2: Residual efficacy of (Clot + Delt) = mixture of Clothianidin 500 g/kg and Deltametrine 62.5 g/kg on mud and cement walls. hr = hour; % = percentage; wks=weeks: IRS= indoor residual spraying

	WKS post IRS	Wall type		Chi-square test
		Cement wall	Mud wall	
1hr knockdown	2wks post IRS	54.3%	10%	<0.001
	6wks post-IRS	35.1%	8%	
	12 wks post-IRS	28.5%	0.7%	
12 hr mortality	2wks post IRS	68.3%	18.7%	<0.001
	6wks post-IRS	59.5%	26.0%	
	12 wks post-IRS	38.4%	9.3%	
24 hr mortality	2wks post IRS	78.4%	34%	<0.001
	6wks post-IRS	68.1%	30.7%	
	12 wks post-IRS	47.1%	18.7%	

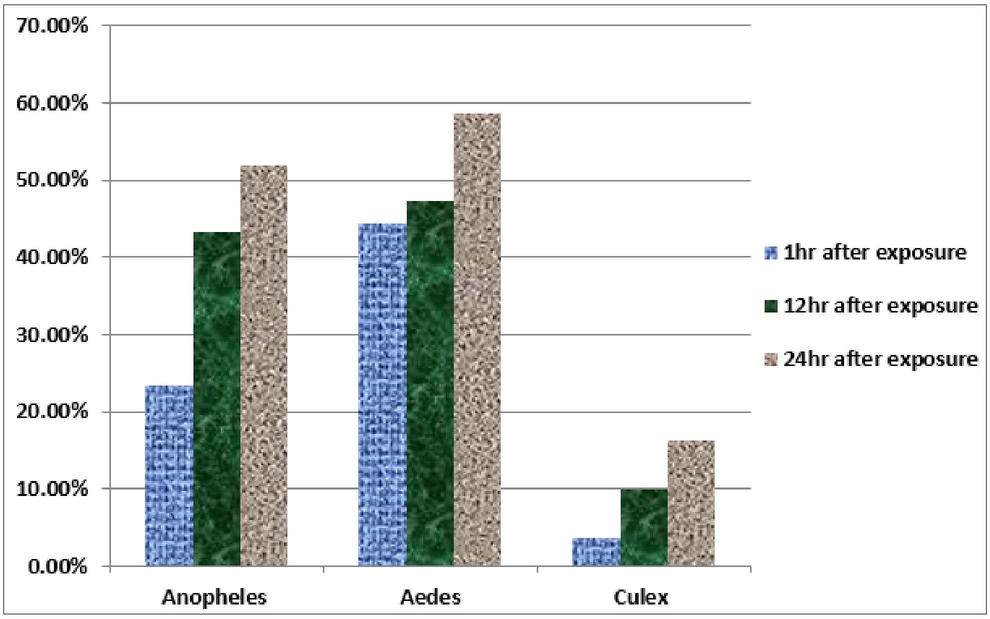

Fig. 1 Mean mortality rates at different time points for the three Types of mosquitoes over the whole study period (combined data for both cement and mud walls). HR = hour; % = percentage

This study also marked the first cone test of Culex and Aedes aegypti on a sprayed wall in Eritrea. Our findings revealed that Culex quinquefasciatus exhibited very low efficacy throughout the study period. Aedes aegypti met the WHO threshold (80%) at two weeks and two months post-spraying, but its efficacy fell below the threshold at three months (58.7%). Additionally, *Anopheles gambiae* exhibited high mortality at two weeks post-spraying, but the formulation failed to kill mosquitoes at two and three months post-spraying. Similar studies in Tesseney district found that Pirimiphos methyl showed high mortality shortly after spraying, but efficacy declined at three months post-spraying [32]. Another bioassay study showed that the residual efficacy of Bendiocarb against Anopheles mosquitoes was 79% at three months post-spraying [33]. In our study, the immediate mortality of Anopheles and Aedes mosquitoes was higher than that of Culex. The residual efficacy of Fludora® Fusion observed in this study (three months) was lower than that observed for *Anopheles culicifacies* s.l. in Gujarat, India [34].

The knockdown effect and delayed mortality of the tested insecticides varied depending on the type of wall. In our study, most households used mud (soil) for construction. This variation in efficacy can be attributed to the differences in porosity between the treated walls [35]. The insecticide solution is absorbed differently by the various wall types, and the bioavailability of the product on these substrates may not remain the same over time [36].

In this study, the residual efficacy of the insecticide formulations was lower on mud walls compared to cement ones, which could be explained by the high porosity of mud, a soil-based material. Previous studies conducted in experimental huts and in the Benin community have shown that residual activity tends to be much lower on highly porous substrates [37, 38]. The better performance observed on cement substrates could be due to the difference in texture between the two materials, with mud being more porous than cement [39]. It has been shown that the nature of the substrate plays a crucial role in the long-term efficacy of IRS treatments [40-42].

As urbanization progresses in many African contexts, with improvements in housing quality-particularly the use of cement and other finished materials-IRS operations using Fludora® Fusion may show greater utility in these settings. However, it is important to note that mosquito exposure in cone bioassays is artificial and does not fully replicate natural conditions.

Conclusions

The study demonstrated that Fludora® Fusion exhibited residual efficacy against Anopheles and Aedes mosquitoes, with mortality rates meeting the WHO threshold of 80% at two months post-spraying. However, the residual efficacy of Fludora® Fusion against these mosquito species decreased by 24% at three months. On the other hand, the residual efficacy of Fludora® Fusion against Culex mosquitoes was consistently low throughout the study period. Given that the efficacy of this new formulation lasted for at least three months, it suggests that a second round of IRS would be advisable in the area, considering the extended transmission period of malaria and other vector-borne diseases.

Abbreviation	Full Form
IRS	Indoor residual spray
LLIN	Long lasting impregnated net
GPS	Geographical positioning system
HMIS	Health management information system
NMCP	National Malaria Control Program
RH	Relative humidity
WHO	World Health Organization
WP	Wettable powders
WG	Water-dispersible granules

Authors' Contributions

AMG wrote the manuscript for publication. AMG, AMW, and IYS contributed to the study design and data collection. AMG and ZZ participated in data analysis. AMG, ZZ, AMW, and IYS critically reviewed the manuscript for intellectual content. All authors have read and approved the final manuscript.

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Availability of Data and Materials

The data used and/or analyzed during this study are available from the corresponding author upon reasonable request.

Ethical Approval and Consent

The study was conducted following the approval of the proposal by the zonal and national research health committees. Written informed consent was obtained from each participating household, ensuring privacy and confidentiality throughout the data collection process. There were no hazardous procedures that posed risks to the participating households.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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