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Determination of the residual efficacy of broflanilide (VECTRON™ T500) insecticide for indoor residual spraying in a semi-field setting in Ethiopia

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Abstract

Background The rotational use of insecticides with diverse modes of action in indoor residual spraying (IRS) is pivotal for enhancing malaria vector control and addressing insecticide resistance. A key factor in national malaria vector control/elimination programmes is the rate at which these insecticides decay. VECTRON™ T500, with broflanilide as its active ingredient, is a recently developed candidate insecticide formulation which has shown promising results in certain phase II experimental hut trials. However, its residual efficacy across different settings has not been thoroughly investigated. This study evaluated the efficacy of VECTRON™ T500 on various wall surfaces (mud, dung, paint, and cement) and assessed its decay rates over time in Ethiopia.

Methods Insectary-reared *Anopheles arabiensis* Sekoru strain mosquitoes were used to evaluate the residual efficacy of VECTRON™ T500. Female mosquitoes, aged three to five days were used for the bioassays. Seven 'tukul' type test huts, each hut with a distinct wall type (mud, dung, painted, and cemented) were used for the study. Three huts received VECTRON™ T500; three huts were sprayed with Actellic 300CS, and one hut served as a negative control (sprayed with water only).

Results VECTRON™ T500 induced over 80% mortality across all wall surface types throughout the entire nine-month study period. In contrast, Actellic® 300CS achieved over 80% mortality for six months, except on dung wall surfaces, after which its efficacy declined sharply below 80%.

Conclusion Overall, the mortality rates achieved with VECTRON™ T500 extended up to nine months across all treated wall surface types, outperforming Actellic® 300CS. This could make VECTRON™ T500 a promising candidate insecticide formulation for use in IRS in malaria-endemic countries such as Ethiopia.

Keywords VECTRON™ T500, Broflanilide, Residual efficacy, Indoor residual spraying, Ethiopia

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Background

Malaria remains a global health challenge, with 249 million cases and 608,000 deaths reported in 2023. Of these fatalities, 67% occurred among children under the age of five [1]. In Africa alone, the World Health Organization (WHO) reported approximately 233 million malaria cases and 580,000 deaths in 2022 [1]. Beyond the toll on human lives, malaria inflicts significant economic burdens [2].

Current malaria control measures primarily depend on early detection and appropriate treatment of cases, and vector control interventions. Vector control, especially through the use of long-lasting insecticidal nets (LLINs), indoor residual spraying (IRS) and larval source management (LSM), aims to reduce vector population densities and human-vector contact [1]. The widespread deployment of LLINs and IRS has contributed to the reduction of malaria incidence and mortality in sub-Saharan Africa over the past two decades [1, 3, 4].

Ethiopia, like many African nations, is endemic to malaria with 60% of its population is at risk of infection. The geographical and climatic conditions in Ethiopia foster conducive environments for malaria vector reproduction [5]. A retrospective study spanning 16 years (2000–2016) revealed persistently high malaria burdens, with over five million cases and thousands of deaths annually [6]. To combat this, various intervention strategies, including IRS, early diagnosis, prompt treatment, and insecticide-treated mosquito nets, are being implemented [7]. Historically, IRS played a pivotal role in the global malaria eradication campaign, leading to the elimination of malaria from Europe and several countries in the Americas and the Caribbean during the 1950s and 1960s [8]. Increased IRS coverage over the last two decades has correlated with reductions in malaria morbidity and mortality in endemic countries across Africa and Asia [9].

However, the efficacy of malaria control programmes is increasingly challenged by the emergence and spread of insecticide resistance within the major mosquito vector species [10, 11]. To address this, the Global Plan for Insecticide Resistance Management (GPIRM) recommends the rotation of non-pyrethroid insecticides with different modes of action for IRS in areas where IRS and LLINs are used together [12]. Currently, very few insecticides are listed by the WHO Pre-qualification Unit Vector Control Product Assessment Team (WHO PQT/VCP) for use in IRS, including bendiocarb, chlorfenapyr, clothianidin and pirimiphos-methyl [8]. However, resistance to pirimiphos-methyl and suspected resistance to chlorfenapyr and clothiandin has been detected in several *Anopheles* mosquito populations in Africa [13–15]. Hence, there is a critical need to identify additional alternative insecticides with novel modes of action.

Broflanilide (trade name TENEBENAL™) belongs to the meta-diamide class of insecticide (IRAC class 30: which targets the GABA-gated chloride channel in the nervous system of insects [16]. With its distinct mode of action, broflanilide holds significant potential for vector control in public health and agriculture [17, 18]. Laboratory and semi-field experimental hut studies conducted in Africa [19–22] showed VECTRON™ T500's potential to provide better and extended control of *Anopheles gambiae* sensu lato (s.l.) and *Anopheles arabiensis*. Moreover, insecticide susceptibility bioassay results have also shown the absence of cross-resistance to broflanilide from mechanisms of resistance to other insecticides in malaria vectors [19, 23, 24]. However, before introducing new vector control products like VECTRON™ T500 to a malaria endemic setting for vector control, it is essential to determine its residual efficacy in diverse wall surface types in various eco-epidemiological settings of malaria endemic countries including Ethiopia. Thus, this study was designed to evaluate the dose, efficacy, and residual activity of VECTRON™ T500 against the Sekoru strain *of An. arabiensis* on different wall surface types in Ethiopia.

Methods

Study area and period

Jimma is the biggest city in the southwest of Ethiopia and home to a population of over 207,500 people. It is situated at 1780 m above sea level. Its economy is varied, and Jimma University (JU), one of Ethiopia's biggest universities, is located there. Beginning in March 2021 to August 2022, the determination of the residual efficacy of broflanilide (VECTRON™ T500) was carried out at JU Tropical & Infectious Diseases Research Center (TIDRC) in Sekoru district, southwest Ethiopia.

Treatment

The study included three treatment groups: VECTRON™ T500, Actellic 300CS (positive control), and water (negative control). The novel IRS product evaluated was VECTRON™ T500. Wall surface types, allowed to completely dry for at least one month, underwent preparation to stabilize pH and, reflect the diverse Ethiopian house building materials. Surface types included: mud, dung, paint and cement. The trial was with three treatments and four wall surfaces, a minimum of 12 treatment surface combinations.

Spray mixture preparation

VECTRON™ 500, containing the active ingredient broflanilide, was mixed according to specified doses. The trained operator used a back-pack sprayer, consistent with WHO specifications [25]. The sprayer was fitted with flat fan nozzles (8002E) and a red control flow valve (CFV). The insecticide was prepared according to the manufacturers manual instructions, with a target dose of 100 mg/m^2 for VECTRON™ T500. The insecticide was applied to a surface area of 250 m^2. Similarly, Actellic 300CS was sprayed by the same trained operator following the manufacturer's manual.

Assessment of insecticidal spray quality

Filter papers (Whitman No. 4) were fixed to each wall surface type at three different heights (high, middle and low) to assess spray quality, with careful labelling and storage for subsequent analysis using high-performance liquid chromatography (HPLC) at the Liverpool School of Tropical Medicine (LSTM).

Assessment of residual activity

WHO cone bioassays were conducted to evaluate the residual efficacy of insecticides on sprayed walls. A susceptible strain of *An. arabiensis*, maintained for over 40 years and susceptible to pyrethroids, organophosphates, and carbamates, was used.

In each hut and on each surface type, three cones were fixed with small nails at different heights: high (50 cm from the junction with the ceiling), middle, and low (50 cm above the floor). Mouth aspirators (separately used for each insecticide) were used to transfer mosquitoes from each paper cup into the cones. After 30 min of exposure, the mosquitoes were put back in their respective paper cups and kept in a wooden box covered with a moist towel, provided with a sugar solution on cotton wool. Subsequently, all the cones were removed from the wall surfaces until the next round of bioassays. Mortality was recorded 24 h post exposure for three consecutive days.

Mosquitoes

Insectary-reared susceptible female *An. arabiensis*, Sekoru strain, aged three to five days old and fed on 10% sugar solution, was used for the bioassays. This strain is known to be susceptible to organochlorines, organophosphates, carbamates, and pyrethroids. To ensure the strain's susceptibility to these four classes of insecticides, susceptibility tests were performed quarterly using the WHO tube assay [26]. In tests conducted three months before the beginning of the evaluation, the strain was found to be susceptible to DDT, deltamethrin, propoxur, and pirimiphos-methyl. The study utilized a total of 840 mosquitoes per month.

Hut design

Seven 'tukul' type experimental huts at TIDRC were renovated and utilized for the study. These circular huts, constructed using the wattle and daub technique, featured walls demarcated as mud, dung, painted, and cemented. Uniform spraying was conducted by experienced spray man, with treatments assigned at randomly (Fig. 1).

Study design

Bioassays were conducted monthly in each hut over a period of nine months until the mean mosquito mortality rate to VECTRON™ T500 declined below 80% for two consecutive months across the treated huts.

Data analysis

Monthly mosquito mortality data were recorded on pre-prepared data sheets, entered into an Excel spreadsheet,

Fig. 1 Experimental huts at Tropical and Infectious Diseases Research Center (TIDRC), Jimma University, Ethiopia

and stored in a Dropbox folder at the Tropical and Infectious Diseases Research Center, Jimma University (JU-TIDRC). The data were analysed based on the number of months post-treatment and the type of treated substrate. Residual efficacy of the insecticide formulations was deemed satisfactory if mortality rates met or exceeded 80%, in line with WHO criteria [27]. Initial statistical analysis was conducted descriptively in Excel, after which the data were exported to the R 4.3.2 software package for advanced statistical analysis. Post-exposure knockdown and daily mortality rates over three days were reported as the mean results from cone tests conducted on three replicate surfaces. A Poisson regression model was used to analyse differences in the observed mean mortality across different wall surface types.

Results

Insecticide spray quality/Filter paper data

The results from the filter paper chemical analysis showed variation in insecticide concentration levels across experimental huts. However, most of the experimental huts were treated with an effective dose of the active ingredients within a range of ± 50% for both active ingredients. The only deviation below the target dose was observed for broflanilide on the mud surface in the first hut (Table S1).

Mosquito mortality 24 h post-exposure

The 24 h mean percent mortality rates of *An. arabiensis* mosquitoes that were exposed in WHO cones to the four different wall surfaces treated with either VECTRON™ T500 or Actellic 300CS is shown in Fig. 3. Both VECTRON™ T500 and Actellic 300CS yielded significantly higher mortality rates on each wall surface types. Overall (nine months) 24 h mortality rates across all wall surface types were 86% and 83% for VECTRON™ T500 and Actellic 300CS, respectively.

The 24 h mortality rate of *An. arabiensis* exposed to the Actellic 300CS insecticide formulation was higher for all surface types during the first four months after the application of the insecticide in three of the wall surfaces (cement, dung and mud) then, started to decline after the fifth month of the insecticide application in almost all wall surfaces. The 24 h mortality rates of *An. arabiensis* mosquitoes treated with VECTRON™ T500 were lower for the first two months and gradually increased (except for the month of June 2022) across all wall surfaces. VECTRON™ T500 applied to the cement wall surface type yielded a higher mortality rate (98%) compared to the other surface types whereas painted wall surface type yielded higher mortality (89%) for Actellic 300CS 24 h post exposure (Fig. 2). Overall, mean mortality rates were significantly higher ($p < 0.05$) for VECTRON™ T500 across all surface types. No significant differences were observed between VECTRON™ T500 and Actellic 300CS for dung, mud, and painted surfaces ($p > 0.05$) (Table S2).

Mosquito mortality 48 h post exposure

The mean percentage mortality rates of *An. arabiensis* mosquitoes 48 h post-exposure to four different wall surfaces treated with VECTRON™ T500 and Actellic 300CS is presented in Fig. 3. High mortality rates across all wall surface types were recorded for both insecticides. Over the nine-month period, the overall mortality rates 48-h post exposure for VECTRON™ T500 and Actellic 300CS 98% and 87%, respectively and the difference was

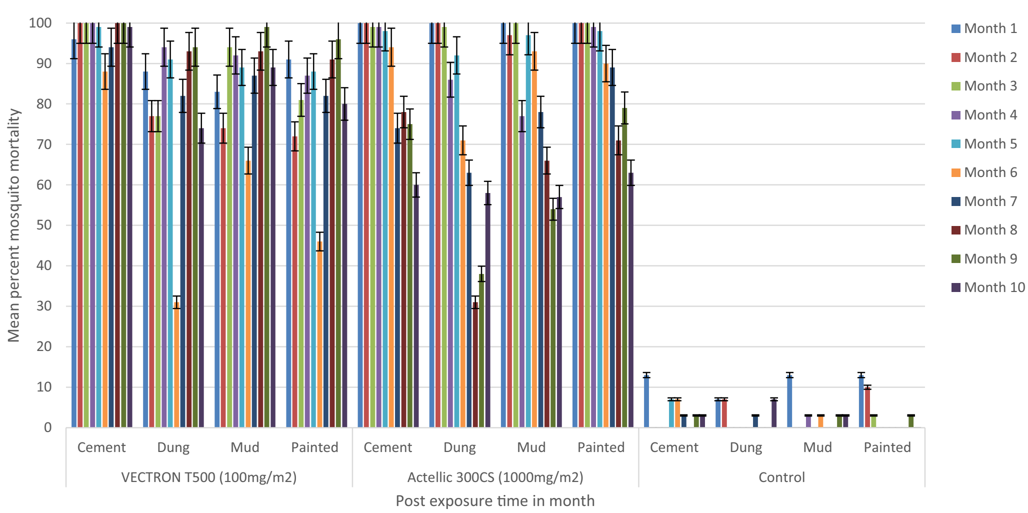


Fig. 2 Mean percentage mortality rates of *An. arabiensis* exposed to different wall surface types treated with VECTRON™ T500 (100mg/m^2) and Actellic 300CS (1000mg/m^2) over time (24 h post exposure)

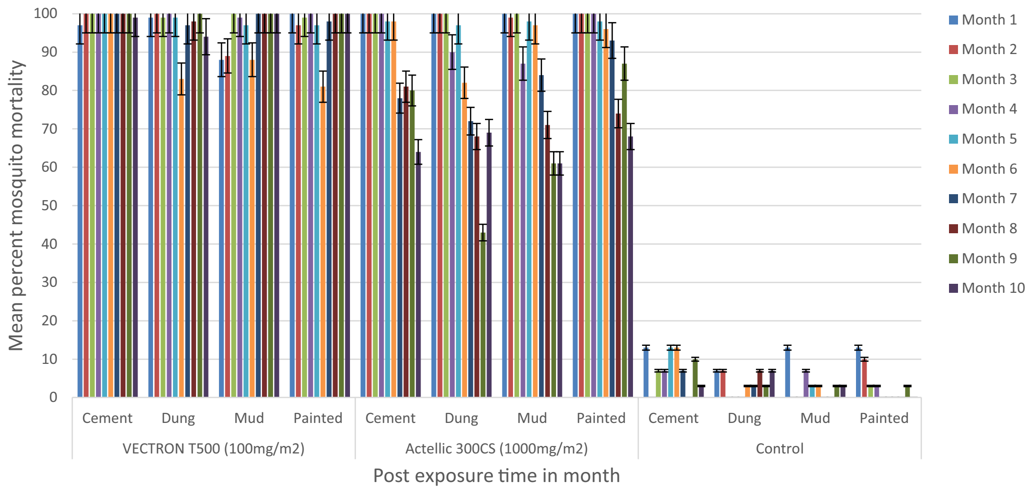


Fig. 3 Mean percentage mortality rates of *An. arabiensis* exposed to different wall surface types treated with VECTRON™ T500 (100 mg/m^2) and Actellic 300CS (1000 mg/m^2) over time (48 h post exposure)

significant ($p < 0.05$). However, no significant difference was observed on mosquito mortality rates on painted wall surfaces sprayed with VECTRON™ T500 and Actellic ($p = 0.244$).

The 48 h mortality rate of *An. arabiensis* exposed to the Actellic 300CS insecticide formulation was higher for all surface types in the first four months after the application of the insecticide in three of the wall surfaces (cement, dung and mud) however, started to decline after the fourth month of the insecticide application in all wall surfaces. The 48 h mortality rates of *An. arabiensis* exposed to wall surfaces treated with VECTRON™ T500 was lower for the first two months and then consistently increased and it was higher than Actellic 300CS across all wall surfaces. VECTRON™ T500 applied to cement wall surface type yielded a relative higher mortality rate (100%) compared to the other surface types, whereas the painted wall surface type yielded a higher mortality (92%) for Actellic 300CS 48 h post exposure (Fig. 3).

Mosquito mortality 72 h post exposure

Mean percent mortality of *An. arabiensis* 72 h post exposure to the four different wall surface types treated with VECTRON™ T500 and Actellic 300CS is presented in Fig. 4. Both VECTRON™ T500 and Actellic 300CS yielded higher mosquito mortality rates across all wall surface types. Over the nine months, the mortality rates at 72 h post exposure rate for all wall surface types for

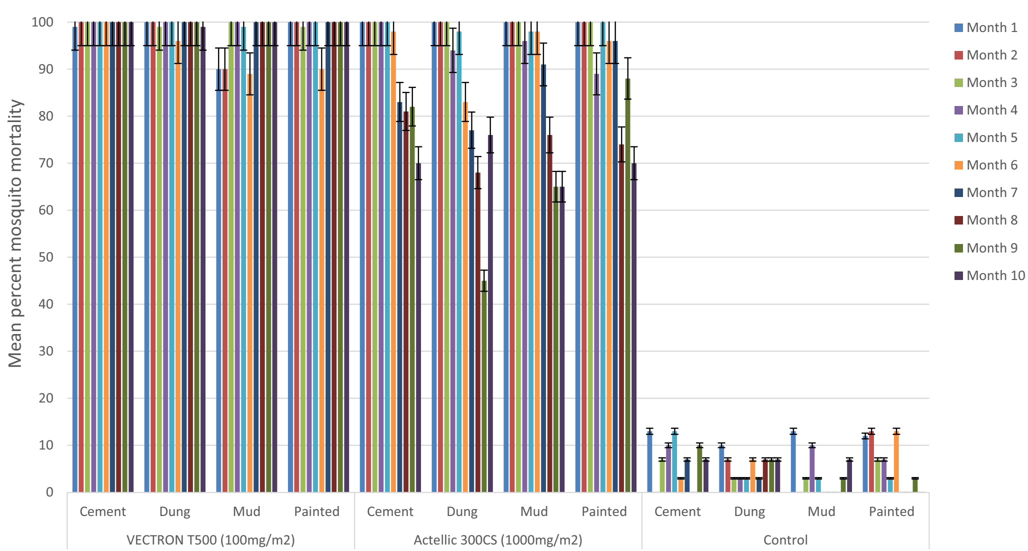


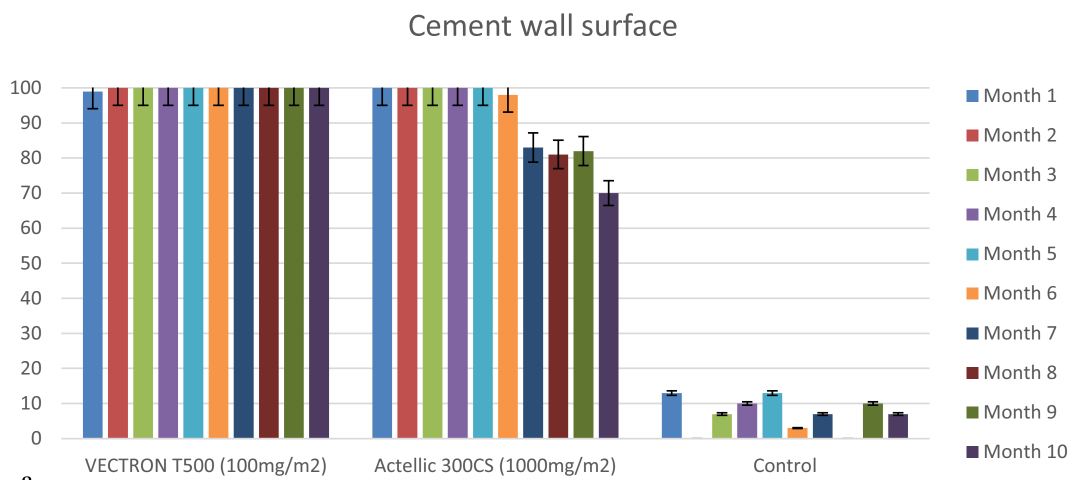
Fig. 4 Mean percentage mortality rates of *An. arabiensis* exposed to different wall surface types treated with VECTRON™ T500 (100 mg/m^2) and Actellic 300CS (1000 mg/m^2) (72 h post exposure)

VECTRON™ T500 and Actellic 300CS was 99% and 89%, respectively. Significant differences in mortality rates were observed on dung wall surfaces sprayed with VECTRON™ T500 and Actellic 300CS at 72 h ($p < 0.05$). No differences in 72 h mortality were observed between VECTRON™ T500 and Actellic 300CS when sprayed on cement, mud, and painted wall surfaces ($p > 0.05$).

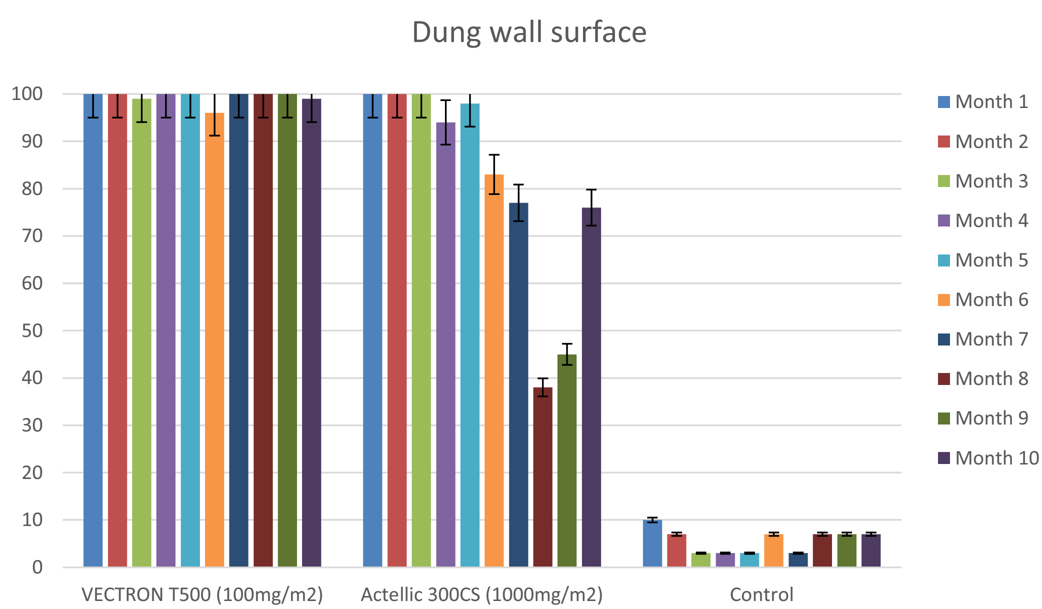
The results of 72 h post exposure mosquito mean mortality from the wall cone bioassays presented in Fig. 5a–d showed that VECTRON™ T500 had a longer residual efficacy on all wall surfaces with mortality remaining above 80% over the nine months period whereas mortality with Actellic CS 300 dropped below 80% (WHO cut-off) after five months. The cement wall surface type yielded a higher mortality rate compared to the other surface types (Fig. 5a).

Discussion

Insecticide resistance remains a major challenge in malaria control and elimination [10, 28, 29]. Implementing insecticide resistance management strategies is crucial for sustaining malaria control efforts. These strategies require the development of novel insecticides with modes of action that effectively target mosquito strains resistant to conventional insecticides [11, 30, 31].

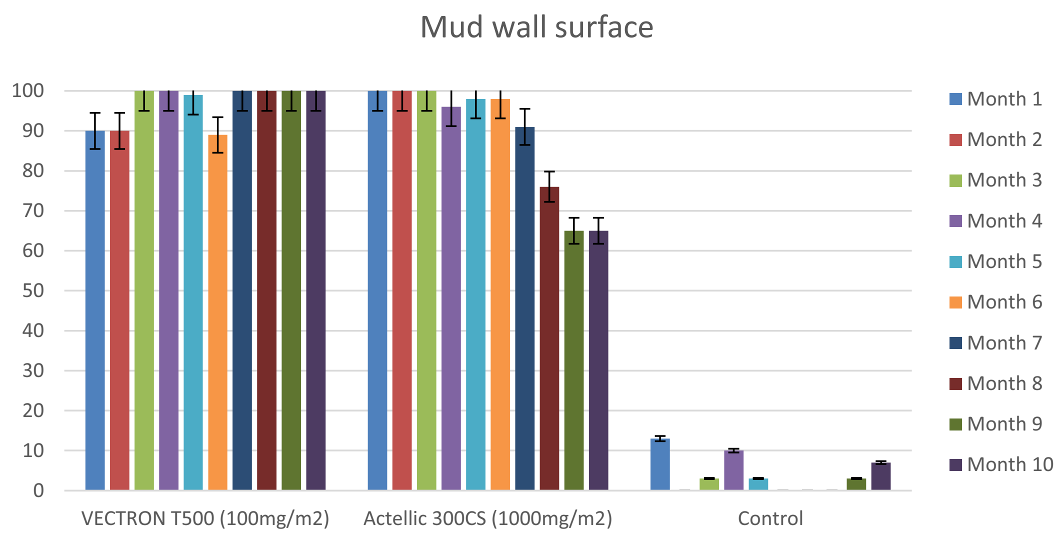


a.

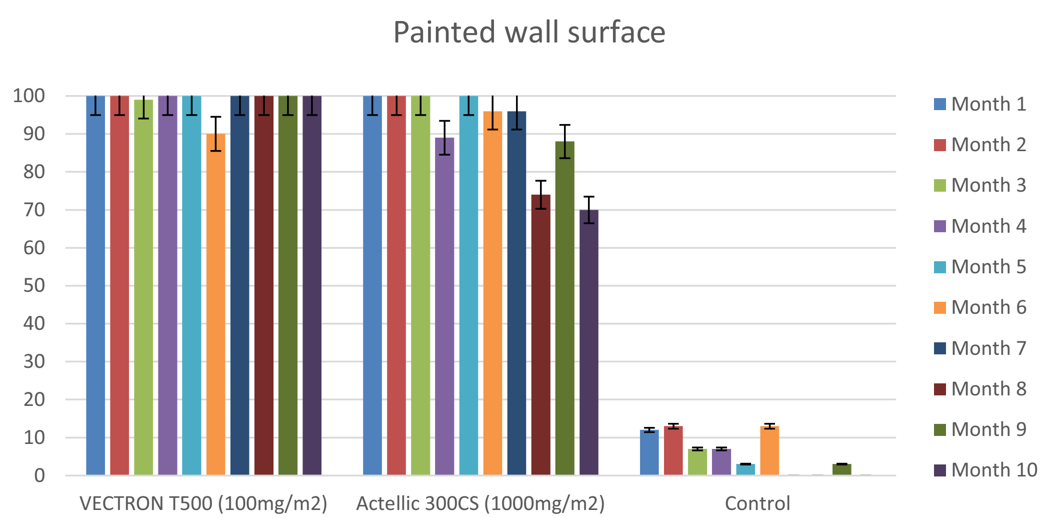


b.

Fig. 5 a–d *An. arabiensis* mean percentage mortality 72 h post exposure from cement, dung, mud and painted wall surface types



c.



d.

Fig. 5 continued

The WHO policy recommendations stipulate that a new IRS insecticide must demonstrate its efficacy against vector mosquitoes, ideally showing non-inferiority to existing IRS products in experimental hut studies [32, 33]. IRS formulations with extended residual efficacy, requiring less frequent application, are more desirable [34]. In this study, VECTRON™ T500 exhibited extended residual efficacy resulting in over 98% mortality for nine months. This study demonstrated longer residual efficacy against *An. arabiensis* susceptible strain and other studies also showed prolonged efficacy VECTRON™ T500 against pyrethroid-resistant populations of *An. gambiae* s.l. in Covè, southern Benin [19] while pyrethroid-resistant *An. arabiensis* in Moshi, Tanzania [21].

In this study, the residual efficacy of VECTRON™ T500 varied across different wall surface types. The highest mortality rate was documented on cement wall surface, followed dung surface. In contrast, the lowest mortality rate was observed on mud surfaces, particularly on the mud wall surface of the first hut. This discrepancy could be due to an issue with the initial spraying, where the spray man might not properly mixed the formulation, resulting in a lower amount of VECTRON™ T500 deposited on the mud surface of first hut. This was confirmed by the results of filter paper analysis using HPLC (Fig. 2). Although most of the experimental huts were treated with the recommended dose of active ingredients, variations in insecticide application rates of up to ± 50% were not uncommon due to the numerous factors involved in the IRS process [35].

Preserving the efficacy of new candidate insecticides is of paramount importance, and the rotational deployment of IRS insecticides with diverse modes of action is recommended for managing insecticide resistance [33]. However, this strategy has been underutilized due to the limited availability of insecticides with different modes of action for IRS. The inclusion of broflanilide (VECTRON™ T500) in the list of WHO PQT/VCP prequalified IRS products will provide a new alternative candidate insecticide to malaria vector control programmes with different mode of action with no observed cross-resistance. This will enhance insecticide resistance management and insecticide of choice for malaria vector control [30].

Although existing evidence demonstrates the efficacy of the product only against susceptible *An. arabiensis* mosquitoes, further research on its residual efficacy against resistant populations of *An. arabiensis* is warranted. An insecticide such as VECTRON™ T500 with longer residual efficacy is needed for IRS and this approach could effectively reduce malaria transmission while minimizing the costs associated with repeated annual IRS operations.

Conclusion

In conclusion, the results of this trial revealed that the residual efficacy of VECTRON™ T500 extended up to nine months which makes it suitable for IRS in Ethiopia where the main malaria transmission season lasts 4–5 months. Moreover, it exhibited longer residual efficacy on the four different wall surface types which are common in Ethiopian houses.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12936-024-05239-9.

Supplementary Material 1.

Supplementary Material 2.

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Author contributions

DY conceived and designed the experiments; HZ performed the experiments; GMK and YGK analysed data; EAS, HZ, TD, EZ and DY wrote the manuscript. All authors read and approved the final manuscript.

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Not applicable.

Data availability

Data generated during the study are available from the corresponding authors up on request.

Declarations

Ethics approval and consent to participate

The study was carried out after obtaining ethical clearance letter (Reference no. 7/2-509/m259/35) from National Research Review Ethics Committee (NRERC), Federal Ministry of Education, Ethiopia.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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