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EFFECT OF PIPERONYL BUTOXIDE (PBO) LONG LASTING INSECTICIDE TREATED NETS (LLINS) ON MALARIA INCIDENCE AND TEST POSITIVITY RATE COMPARED TO STANDARD LLINS AFTER MASS NET CAMPAIGN IN KENYA, 2021
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ABSTRACT

Objective: **This study aimed to compare the effectiveness of Piperonyl Butoxide (PBO) Long -Lasting Insecticidal Treated Nets (LLINs) and standard LLINs on malaria incidence and Test Positivity Rate (TPR).**
Design: **This was a retrospective cross-sectional study using routinely collected data on malaria incidence and test positivity rate in Kenya Health Information System (KHIS) from a county where PBO LLINs and standard LLINs were distributed.**
Setting: **Malaria incidence and positivity rate data from Siaya and Busia counties where standard LLINs and PBO LLINs were distributed respectively was extracted from KHIS. The two counties are within Lake endemic zone with malaria prevalence at 19% and high intensity of insecticide resistance.**
Interventions: **Deployment of PBO and standard LLINs.**
Main outcome measures: **Malaria incidence and test positivity rate.**

Results: **Malaria incidence decreased from 612.8 cases in 2020 to 590.5 cases in 2021 and TPR decreased from 54.6% in 2020 to 47.4% in 2021 after the distribution of standard LLINs. In Busia where PBO LLINs were distributed, Malaria incidence increased from 436.9 cases in 2020 to 525.4 2021 after distribution due to increased blood examination rate from 84 per 100 populations to 106.3 per 100 populations in 2021. Test positivity rate decreased from 48.3% in 2020 to 43.1% in 2021 after distribution of PBO.**

Conclusion: **The PBO LLINs were more effective than standard LLINs in reduction of malaria incidence and test positivity rate in an area with high intensity of pyrethroid resistance.**

INTRODUCTION

Malaria remains a major public health problem worldwide, with 247 million cases and 619,000 deaths reported in 2021(1). More than 90% of these cases and deaths are reported in sub-Saharan Africa. Kenya has reported a substantial decrease in malaria prevalence from 11% in 2015 to 6% in 2020(2)(3). The highest burden of malaria in Kenya is reported in Lake endemic zone at 19% and the coast endemic zone at 6%. The decrease in malaria burden in Kenya over time is attributable to the implementation of preventive interventions mainly, Long Lasting Insecticide Treated Nets (LLINs), Indoor Residual Spraying (IRS), use of artemisinin-based combination therapy (ACTs) among others.

The use of LLINs in malaria control has been shown to avert about 68% of malaria cases when compared with other malaria interventions(4). The effectiveness of LLINs is due to their ability to act as a physical barrier hence preventing mosquitos from getting into contact with human beings. Additionally, LLINs provide a chemical barrier since it is impregnated with an insecticide (pyrethroid) which kills or knocks down mosquitos. Continued use of pyrethroids in LLINs has led to insecticide resistance in *Anopheles* spp mosquitos, which is the main malaria vector, rendering the pyrethroid-only LLINs less effective. Pyrethroid resistance occurs mainly through two mechanisms; knockdown resistance due to genetic changes within the voltage-gated sodium channel where pyrethroids bind, and metabolic resistance due to changes in enzymes (cytochrome P450s) that detoxify pyrethroids.

Insecticide resistance to pyrethroid use in nets is widespread in Africa (5).In Kenya insecticide resistance to pyrethroids used in LLINs has been reported in almost all the malaria epidemiological zone (6). Studies conducted in Kenya in the malaria lake endemic zone and coast endemic zone not only indicate widespread resistance to pyrethroids but in high intensity(7). In response to the rapid spread of pyrethroid resistance across Africa, the World Health Organization (WHO) has encouraged manufacturers to develop new types of LLINs that contain active ingredients with new modes of action to address the problem (8). Piperonyl Butoxide (PBO) is one of the chemicals that when incorporated in ITNs inhibits enzymes that are responsible for detoxification of the pyrethroid before the neurotoxin reacts with its target site.

Kenya has aligned its vector control intervention with global strategies for the management of insecticide resistance. One of these strategies is deployment of PBO LLINs.

In Kenya, the distribution of LLINs through the mass campaign is conducted after every 3 years in 27 counties in different malaria epidemiological zones. The country has been distributing pyrethroid-only nets (standard LLINs). In the 2020 mass net campaign, PBO LLINs were introduced in three counties; Kakamega, Busia, and Bungoma within the lake endemic zone as a strategy for the management of insecticide resistance, the rest of the counties received standard LLINs (contains pyrethroid only). Evidence on the effect of PBO LLIN compared with standard LLINs on malaria burden in Kenya after the mass net campaign has not been generated. The aim of this study was to document the effect of standard LLINs and PBO LLINs on malaria incidence and test positivity rate and compare their effect post-distribution.

MATERIALS AND METHODS

Study Design

This was a retrospective cross-sectional study using routinely collected data in Kenya Health Information System (KHIS). Two–year (2019 and 2021) retrospective data on malaria incidence and test positivity rate from one county where PBO LLINs were distributed and one county where standard LLINs were distributed was extracted from KHIS and compared with two-year data post-distribution (2021 and 2022).

Study Setting

The study was conducted by extracting data for two counties within the lake endemic zone namely, Busia and Siaya. In Busia, PBO LLINs were distributed and in Siaya standard LLINs were distributed. The lake endemic zone is within the Lake Victoria region where the altitude is between 0 to 1300 meters. Malaria transmission in this zone is perennial. The high temperatures in this zone favor the sporogonic cycle (*Plasmodium spp* cycle with the mosquito) while the rainfall creates the breeding sites for malaria vectors. High intensity of insecticide resistance to pyrethroid has been reported in this zone.

Study Population

Malaria Cases from health facilities data in Busia (PBO LLINs) and Siaya (standard LLINs) counties.

Variables

The main outcome variables were malaria incidence and test positivity rate. The independent variable was type of LLIN.

Data collection Procedure

Data on malaria incidence was extracted from KHIS (accessed 28th August 2023).

Analysis and Statistics

Malaria incidence in Busia and Siaya counties before and after the mass net campaign 2020/2022 was downloaded from KHIS. Malaria incidence was calculated as number of confirmed malaria cases per 1000 population. The test positivity rate was calculated as number of positive malaria cases divided by the total number tested. Data was then disaggregated by months and type of LLIN distributed.

Ethical Approval

Ethical clearance was obtained from the Maseno University Scientific and Ethics Review Committee (approval number MUSERC/01234/23). Permission to use the assessment data was sought from National Malaria Control Program (NMCP).

RESULTS

The coverage for PBO and conventional LLINs was 99.8% and 92.2% respectively (Table 1). The annual malaria incidence in Siaya before distribution of standard ITNs in 2019 and 2020 was 717.2 and 612.8 cases respectively. This decreased to 590.5 confirmed cases per 1000 population after distribution of standard ITNs and an increase to 703.7 cases one year after distribution of ITNs (Table 2). The annual malaria test positivity rate decreased from 53.9% in 2019 and 54.6% in 2020 before distribution of ITNs to 47.4% in 2021 and 52.9% in 2022 after distribution.

Table 1

ITNs coverage in Busia and Siaya counties-source mass net 2020/2021 report

Type of ITN	County	ITNs required	Nets coverage n, (%)
PBO	Busia	641,153	99.8%, (639,850)
Conventional	Siaya	678,382	92.2%, (625,480)

Table 2

Annual Malaria incidence, Test positivity rate and Blood Examination Rate before (2019-2020) and after distribution of standard ITNs (2021-2022) in Siaya County

	2019	2020	2021	2022
Annual Malaria Blood Examination Rate	117.2	99.5	108.2	116.6
Annual Confirmed Malaria Cases Per 1000 Population	717.2	612.8	590.5	703.7
Annual Malaria test positivity rate %	53.9%	54.6%	47.4%	52.9%

The monthly trends on malaria incidence and test positivity rate from 2019 to 2022 showed malaria peaks in the months of May and June during the long rains and October to December during the short rains (Figure 1). The monthly malaria incidence and test positivity rate was lower in 2021 after distribution of standard ITNs compared with 2019 monthly incidence and test positivity rates.

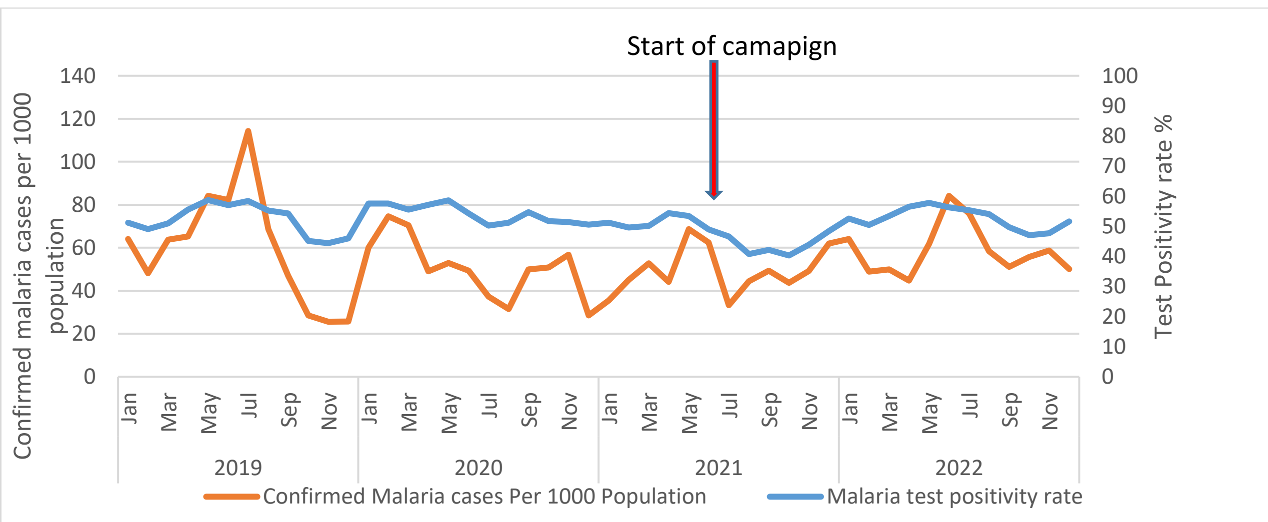


Figure 1: Monthly trends in malaria incidence and test positivity rates in Siaya County-2019-2022

In Busia County where PBO ITNs were distributed, the annual malaria incidence decreased from 660.2 in 2019 to 525.4 in 2021.

However, malaria incidence increased to 648.8 cases per 1000 population in 2022, one year after distribution of PBO ITN. There was a decrease in test positivity rate in Busia County from 52.8% in 2019 before distribution of PBO to 43.1%, in 2021 after distribution of PBO and a year later (2022) at 41.4% (Table 3).

Table 3: Annual Malaria incidence, Test positivity rate and Blood Examination Rate before (2019-2020) and after distribution of PBO ITNs (2021-2022) in Busia County

	2019	**2020**	**2021**	**2022**
Annual Malaria test positivity rate	52.8	48.3	43.1	41.4
Annual Malaria Blood Examination Rate	117.8	84	106.3	118.9
Annual Confirmed Malaria cases Per 1000 Population	660.2	436.9	525.4	648.8

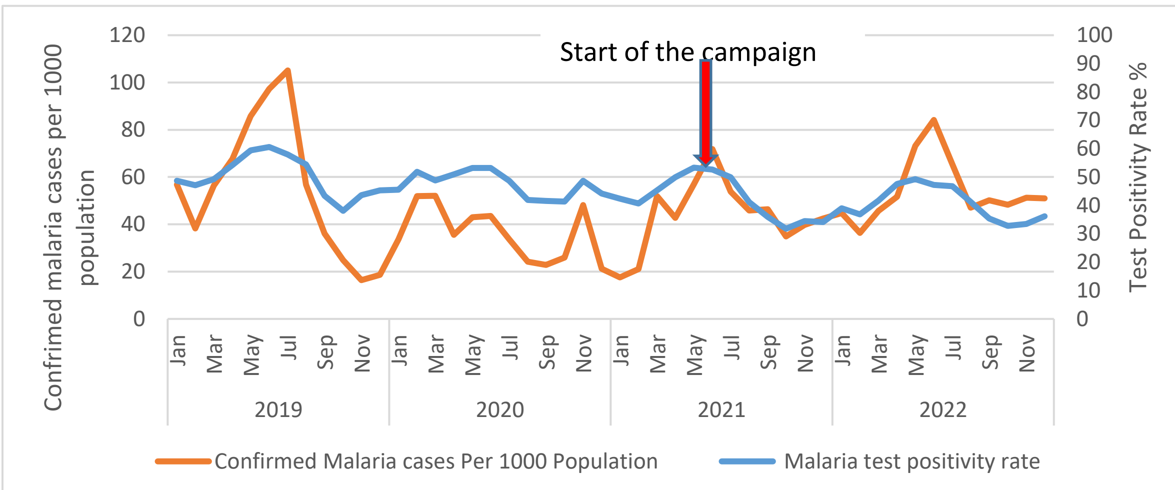
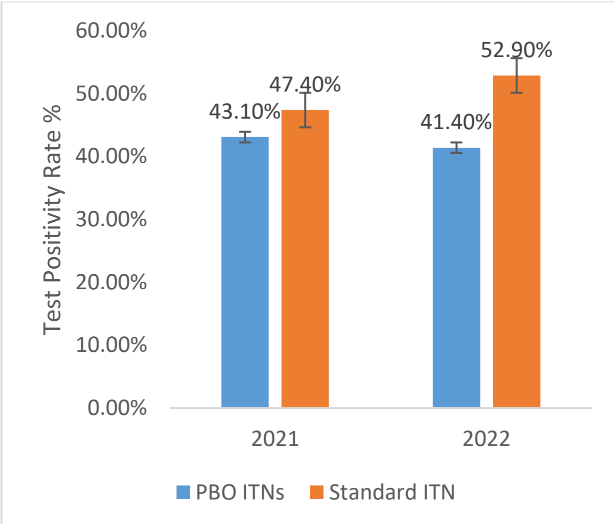


Figure 2: Monthly trends in Malaria incidence and Test Positivity rate in Busia County, 2019-2022

The was an increase in malaria incidence and test positivity during the months of May to June (long rains) and October to December (short rains). After distribution of PBO ITNs in Busia in June 2021, the monthly malaria incidence and test positivity rate decreased up to May 2022 which is the peak malaria period (Figure 2).

The annual test positivity rate in 2021 and 2022 after distribution of PBO ITNs was 43.10% and 41.40% respectively. This was less when compared with Test Positivity Rate (TPR) after distribution of standard only nets at 47.40% and 52.90% in 2021 and 2022 respectively (Figure 3a). The annual malaria incidence was lower after distribution of PBO ITNs at 524 and 649 cases per 1000 population in 2021 and 2022 when compared with standard ITNs at 591 and 704 cases per 1000 population in 2021 and 2022 respectively.



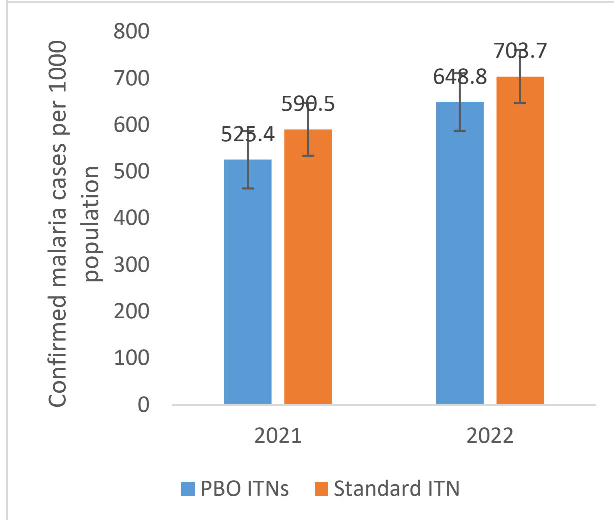


Figure 3a *Figure 3b*

Figure 3and 3b: Comparison in annual malaria test positivity rate and malaria incidence after distribution of PBO and standard ITNs

The monthly trend in TPR after the distribution of PBO LLINs was lower when compared with standard ITNs up to about one and a half years (Figure 4).

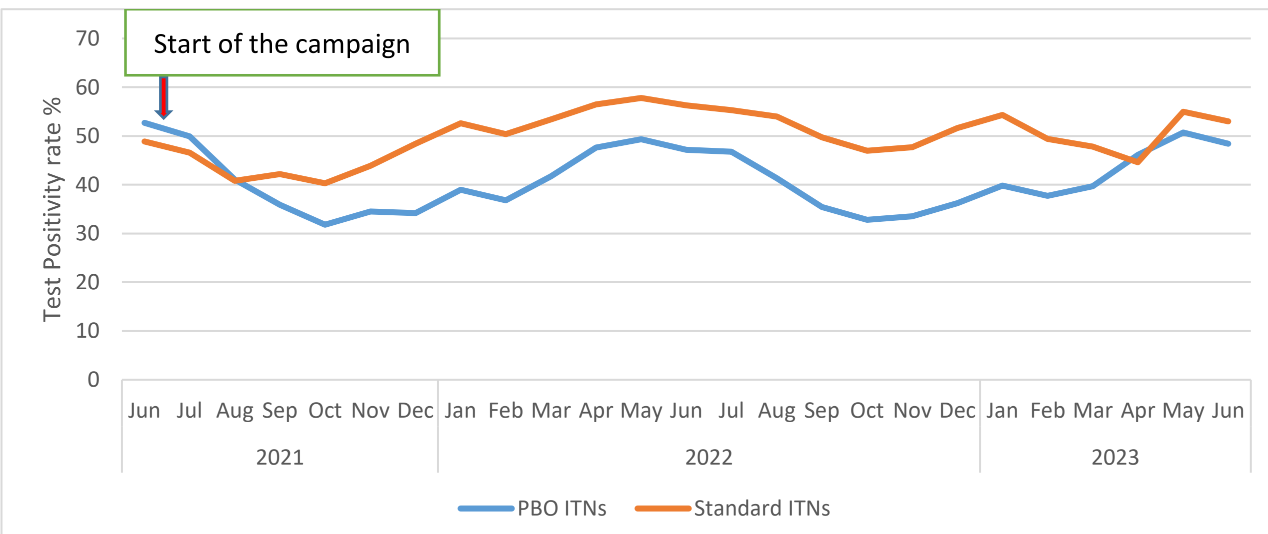


Figure 5: Comparison in Monthly Trends in Test positivity rate- PBO vs Standard ITNs, June 2021-June 2023

DISCUSSION

This study compared the effectiveness of PBO LLINs and standard LLINs on malaria incidence and test positivity rate after mass net distribution in June 2021. Based on the findings of this study both PBO and standard LLINs were effective in reduction of annual malaria incidence and TPR. When compared, PBO ITNs were more effective than standard LLINs up for not more than two-years post distribution.

Before distribution of PBO and standard LLINs annual TPR was high and reduced after distribution up to 2 years. Malaria incidence on the other hand decreased but after one year of distribution increased to levels almost like 2 years before distribution. This could be attributable to the increased annual blood examination rate which indicates high testing rates probably due to availability of commodities, community case management/testing among others. In this regard, annual malaria incidence was interpreted in relation to annual blood examination rate. These findings are consistent with a study conducted in Western Kenya which showed that use of LLINs led to decline in malaria test positivity rate(9). Studies conducted in Burundi and Madagascar showed a steep decline in malaria incidence one year after distribution of LLINs (10)(11). The monthly trends of malaria incidence and TPR decreased after distribution of LLINs with peaks between May and June and October to December which coincides with the long rains and short rains period. In East Africa, previous studies have shown similar findings on malaria seasonality with peaks during or immediately after long and short rains(12)(13). However, emerging information shown that malaria seasonality is changing due to climatic change which has led to malaria being reported in new areas and outbreaks (14)(15)(16).

Malaria incidence and test positivity rate was lower where PBO LLINs were distributed compared with areas where standard LLINs were distributed up-to one and a half years post distribution. These findings are indicative of the additive effect of PBO LLINs in areas of high intensity of insecticide resistance compared with standard LLINs in similar settings. A cluster randomized study conducted in Western Kenya showed that PBO LLINs are more superior than standard LLINs in reduction of malaria burden (17). In this study, PBO LLINs reduced malaria incidence and TPR up to one and a half years. This is consistent with durability studies that have been conducted in Kenya and Tanzania showing effectiveness of PBO LLINs is not more 2-years (18)(19). However, if the PBO LLIN with proportionate Hole Index (PHI) of less than 64 can still provide physical protection against mosquitos (20).

This study did not assess factors associated with LLINs use, fabric integrity of LLINs, attrition rate and bio-efficacy of the nets.

Based on the findings of this study, PBO LLINs should be deployed in areas with high intensity of insecticide resistance for not more than two years. Standard LLINs provide physical barrier against mosquito bites and their deployment in an area should be guided by data on insecticide resistance and fabric integrity from durability studies.

CONCLUSION

This the first study in Kenya to evaluate effectiveness of PBO LLINs in comparison with standard LLINs after mass net distribution campaign. The findings of this study indicate that PBO LLINs were more effective in reducing malaria incidence and test positivity rate but for not more than 2 years post distribution. These findings emphasize the importance of deployment of PBO LLINs in areas with insecticide resistance as recommended by WHO. More studies on durability of PBO LLINs should be conducted to supplement the findings of this study.

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