

# Setting greater ambition for malaria prevention with long-lasting insecticidal nets with piperonyl butoxide (PBO LLINs)

Malaria endemic countries applying for Global Fund financing are invited to demonstrate in their concept note a sense of boldness, innovation and ambition in setting targets or designing intervention mixes, and a sense of urgency to quickly “move the needle” towards ending epidemics.

As national malaria control teams engage in an exercise to stratify and target interventions that drive impact, they should consider the following:

**1** Reducing incidence is essential to make progress towards ending malaria. Malaria treatment is expensive and places a heavy burden on health systems, while prevention is cheap.

## Populations in areas with the highest malaria burden stand most to benefit from PBO LLINs

In the World Malaria Report 2019, WHO acknowledges that PBO LLINs provide “improved impact against malaria” and recommends the scale-up of these nets in areas where the main malaria vectors meet the criteria recommended in 2017.

**If countries do not have data on the resistance mechanism, WHO advises they can aim for areas with the highest combined risks of prevalence, incidence and mortality.**

In particular, pregnant women and children under five are critical populations to be protected. The World Malaria Report 2019 highlights that overall coverage for pregnant women and children in sub-Saharan Africa has improved only marginally since 2015: an estimated 39% of pregnant women and children under five did not sleep under an insecticide-treated mosquito net in 2018 and an estimated 11 million pregnant women – 29% of all pregnancies – were infected with malaria in 2018.

**2** In a resource-constrained environment, we need to do more than to simply scale-up existing interventions.

**3** We need to be mindful of the extra complexity brought by new interventions and their demands on the health system, as well as of the value-for-money of selected interventions.

All people at risk of malaria should be protected with the most effective intervention: PBO LLINs are a highly cost-effective intervention which can help bolster prevention targets and make a dent in the malaria burden. We argue that PBO LLINs should become the standard of care in all areas of pyrethroid resistance and call for a rapid shift to PBO LLINs.



## PBO LLINs can drive impact to decrease malaria incidence and prevalence

Compared to a pyrethroid-only net, a PBO LLIN has an increased killing effect on malaria vectors that have overexpressed monooxygenase-based resistance mechanisms and more effectively reduced malaria prevalence.

A randomized controlled study conducted in Tanzania<sup>1</sup> showed that PBO LLINs were more effective than the standard pyrethroid LLINs in reducing malaria infection prevalence in an area of high usage of these nets and high pyrethroid resistance in the primary malaria vectors. The additional effect of the PBO LLINs on malaria prevalence was evident at the end of the first year with 44% fewer malaria cases and at the end of the second year with 33% fewer malaria cases compared with the standard pyrethroid LLINs.

These findings were supported by the entomological outcomes, which showed a significant reduction in malaria transmission with entomological inoculation rates (number of malaria infected mosquitoes captured per house) being reduced by 87% during the first year and 67% during the second year in areas receiving PBO long-lasting insecticidal nets compared with standard long-lasting insecticidal nets.

A second cluster randomised trial was implemented to evaluate the impact of LLINs delivered in the 2017–2018 Uganda national LLIN distribution campaign<sup>2</sup>. The results show that both pyrethroid LLINs and PBO LLINs reduced malaria prevalence from baseline. PBO LLINs were more effective, both at killing mosquitoes and at reducing malaria in the population. Specifically, at 6 months, 26% fewer malaria cases were observed in children in the PBO LLIN clusters compared to those in the pyrethroid LLIN arm. After 12 and 18 months, there were 27% and 16% fewer malaria cases detected, respectively. Reported usage of LLINs remained high up to 18 months.

These findings are also supported by secondary study outcomes on mosquito vector density. At 18 months, 75% fewer mosquitoes were collected in the PBO LLIN households than in pyrethroid LLIN households. Overall, in Uganda, where pyrethroid resistance is high, PBO LLINs were more effective at reducing malaria parasite prevalence than pyrethroid LLINs for up to 18 months.

## PBO LLINs offer a new cost-effective solution with a low-level of additional complexity for the health system

Unlike other new prevention tools, PBO LLINs can be distributed through existing routine channels (antenatal care services, school distribution) or mass campaigns, with little extra complexity compared to the distribution of pyrethroid-only LLINs.

Uganda provides an example of a deployment of PBO LLINs at scale: It was the first country to take a bold step to include PBO LLINs in their mass distribution campaign with funding from Against Malaria Foundation. Over 6 million PBO LLINs were deployed as part of the 2017-18 campaign. Uganda was also one of only 2 countries to report a reduction in malaria cases (a drop of 1.5 million cases and about 11% of total cases) in the World Malaria Report 2019.

Evidence suggests that PBO LLINs are more effective in areas with pyrethroid resistant malaria mosquitoes. Despite the unit cost of PBO LLINs being higher than pyrethroid-only LLINs, modelling studies<sup>3</sup> have

suggested that PBO LLINs are highly cost-effective. (The incremental price increase compared to a pyrethroid LLIN has been reduced to less than USD 1). The case for PBO LLINs is even more compelling when taking into account the cost of recurring malaria treatment and the overall cost to the health-system.

<sup>1</sup> Protopopoff N *et al.* Effectiveness of a long-lasting piperonyl butoxide-treated insecticidal net and indoor residual spray interventions, separately and together, against malaria transmitted by pyrethroid-resistant mosquitoes: a cluster, randomised controlled, two-by-two factorial design trial. *Lancet*. 2018. 391: 1577–88. [https://doi.org/10.1016/S0140-6736\(18\)30427-6](https://doi.org/10.1016/S0140-6736(18)30427-6)

<sup>2</sup> Staedke, S *et al.* LLIN Evaluation in Uganda Project (LLINEUP) – Effect of long-lasting insecticidal nets (LLINs) with, and without, piperonyl butoxide on malaria indicators in Uganda: a cluster-randomised trial embedded in a National LLIN Distribution Campaign (November 22, 2019). Available at SSRN: <https://ssrn.com/abstract=3491911>

<sup>3</sup> Churcher *et al.* (2016). The impact of pyrethroid resistance on the efficacy and effectiveness of bednets for malaria control in Africa. *eLife* 5:e16090.

Shepard, D. *et al.* (2017). Cost-effectiveness of pyrethroid plus PBO bed nets compared to pyrethroid-only nets: results from a controlled epidemiological study in Nigeria. Manuscript in prep.

Farlow, R. *et al.* (2017). VecNet model simulations of the impact of PermaNet® 2.0 versus PermaNet® 3.0 against pyrethroid resistant *Anopheles gambiae* transmission of *P. falciparum* malaria. Manuscript in prep.

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