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[Intervention Review]

Piperonyl butoxide (PBO) combined with pyrethroids in insecticide-treated nets to prevent malaria in Africa

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ABSTRACT

Background

Public health strategies that target mosquito vectors, particularly pyrethroid long-lasting insecticidal nets (LLINs), have been largely responsible for the substantial reduction in the number of people in Africa developing malaria. The spread of insecticide resistance in *Anopheles* mosquitoes threatens these impacts. One way to control insecticide-resistant populations is by using insecticide synergists. Piperonyl butoxide (PBO) is a synergist that inhibits specific metabolic enzymes within mosquitoes and has been incorporated into pyrethroid-LLINs to form pyrethroid-PBO nets. Pyrethroid-PBO nets are currently produced by four LLIN manufacturers and, following a recommendation from the World Health Organization (WHO) in 2017, are being included in distribution campaigns in countries. This review examines epidemiological and entomological evidence on whether the addition of PBO to LLINs improves their efficacy.

Objectives

1. Evaluate whether adding PBO to pyrethroid LLINs increases the epidemiological and entomological effectiveness of the nets.

2. Compare the effects of pyrethroid-PBO nets currently in commercial development or on the market with their non-PBO equivalent in relation to:

a. malaria infection (prevalence or incidence);

b. entomological outcomes.

Search methods

We searched the Cochrane Infectious Diseases Group (CIDG) Specialized Register; CENTRAL, MEDLINE, Embase, Web of Science, CAB Abstracts, and two clinical trial registers (ClinicalTrials.gov and WHO International Clinical Trials Registry Platform) up to 24 August 2018. We contacted organizations for unpublished data. We checked the reference lists of trials identified by the above methods.

Selection criteria

We included laboratory trials, experimental hut trials, village trials, and randomized clinical trials with mosquitoes from the *Anopheles gambiae* complex or *Anopheles funestus* group.

Data collection and analysis

Two review authors assessed each trial for eligibility, extracted data, and determined the risk of bias for included trials. We resolved disagreements through discussion with a third review author. We analysed the data using Review Manager 5 and assessed the certainty of the evidence using the GRADE approach.

Main results

Fifteen trials met the inclusion criteria: two laboratory trials, eight experimental hut trials, and five cluster-randomized controlled village trials.

One village trial examined the effect of pyrethroid-PBO nets on malaria infection prevalence in an area with highly pyrethroid-resistant mosquitoes. The latest endpoint at 21 months post-intervention showed that malaria prevalence probably decreased in the intervention arm (OR 0.40, 95% CI 0.20 to 0.80; 1 trial, 1 comparison, moderate-certainty evidence).

In highly pyrethroid-resistant areas (< 30% mosquito mortality), in comparisons of unwashed pyrethroid-PBO nets to unwashed standard-LLINs, PBO nets resulted in higher mosquito mortality (risk ratio (RR) 1.84, 95% CI 1.60 to 2.11; 14,620 mosquitoes, 5 trials, 9 comparisons, high-certainty evidence) and lower blood feeding success (RR 0.60, 95% CI 0.50 to 0.71; 14,000 mosquitoes, 4 trials, 8 comparisons, high-certainty evidence). However, in comparisons of washed pyrethroid-PBO nets to washed LLINs we do not know if PBO nets have a greater effect on mosquito mortality (RR 1.20, 95% CI 0.88 to 1.63; 10,268 mosquitoes, 4 trials, 5 comparisons, very low-certainty evidence), although the washed pyrethroid-PBO nets do decrease blood feeding success compared to standard-LLINs (RR 0.81, 95% CI 0.72 to 0.92; 9674 mosquitoes, 3 trials, 4 comparisons, high-certainty evidence).

In areas where pyrethroid resistance is considered moderate (31% to 60% mosquito mortality), there may be little or no difference in effects of unwashed pyrethroid-PBO nets compared to unwashed standard-LLINs on mosquito mortality (RR 1.16, 95% CI 0.88 to 1.54; 242 mosquitoes, 1 trial, 1 comparison, low-certainty evidence), and there may be little or no difference in the effects on blood feeding success (RR 0.87, 95% CI 0.67 to 1.13; 242 mosquitoes, 1 trial, 1 comparison, low-certainty evidence). The same pattern is apparent for washed pyrethroid-PBO nets compared to washed standard-LLINs (mortality: RR 1.07, 95% CI 0.74 to 1.54; 329 mosquitoes, 1 trial, 1 comparison, low-certainty evidence; blood feeding success: RR 0.91, 95% CI 0.74 to 1.13; 329 mosquitoes, 1 trial, 1 comparison, low-certainty evidence).

In areas where pyrethroid resistance is low (61% to 90% mosquito mortality), there is probably little or no difference in the effect of unwashed pyrethroid-PBO nets compared to unwashed standard-LLINs on mosquito mortality (RR 1.10, 95% CI 1.05 to 1.16; 708 mosquitoes, 1 trial, 2 comparisons, moderate-certainty evidence), but there is no evidence for an effect on blood feeding success (RR 0.67, 95% CI 0.06 to 7.37; 708 mosquitoes, 1 trial, 2 comparisons, very low-certainty evidence). For washed pyrethroid-PBO nets compared to washed standard-LLINs we do not know if there is any difference in mosquito mortality (RR 1.16, 96% CI 0.83 to 1.63; 878 mosquitoes, 1 trial, 2 comparisons, very low-certainty evidence), but blood feeding may decrease (RR 1.50, 95% CI 0.89 to 2.54; 878 mosquitoes, 1 trial, 2 comparisons, low-certainty evidence).

In areas were mosquito populations are susceptible to insecticides (> 90% mosquito mortality), there may be little or no difference in the effect of unwashed pyrethroid-PBO nets compared to unwashed standard-LLINs on mosquito mortality (RR 1.20, 95% CI 0.64 to 2.26; 2791 mosquitoes, 2 trials, 2 comparisons, low-certainty evidence). This is similar for washed nets (RR 1.07, 95% CI 0.92 to 1.25; 2644 mosquitoes, 2 trials, 2 comparisons, low-certainty evidence). We do not know if unwashed pyrethroid-PBO nets have any effect on blood feeding success of susceptible mosquitoes (RR 0.50, 95% CI 0.11 to 2.32; 2791 mosquitoes, 2 trials, 2 comparisons, very low-certainty evidence). The same applies to washed nets (RR 1.28, 95% CI 0.81 to 2.04; 2644 mosquitoes, 2 trials, 2 comparisons, low-certainty evidence).

In village trials comparing pyrethroid-PBO nets to LLINs, there was no difference in sporozoite rate (4 trials, 5 comparison) and mosquito parity (3 trials, 4 comparisons).

Authors' conclusions

In areas of high insecticide resistance, pyrethroid-PBO nets reduce mosquito mortality and blood feeding rates, and results from a single clinical trial demonstrate that this leads to lower malaria prevalence. Questions remain about the durability of PBO on nets, as

the impact of pyrethroid-PBO LLINs on mosquito mortality was not sustained over 20 washes in experimental hut trials. There is little evidence to support higher entomological efficacy of pyrethroid-PBO nets in areas where the mosquitoes show lower levels of resistance to pyrethroids.

PLAIN LANGUAGE SUMMARY

Pyrethroid-PBO nets to prevent malaria

Background

Bed nets treated with pyrethroid insecticides are an effective way to reduce malaria transmission and have been deployed across Africa. However, mosquitoes that spread malaria are now developing resistance to this type of insecticide. One way to overcome this resistance is to add another chemical, piperonyl butoxide (PBO), to the net. PBO is not an insecticide but blocks the substance (an enzyme) inside the mosquito that stops pyrethroids working.

What is the aim of this review?

The aim of this Cochrane Review was to find out if pyrethroid-PBO nets add additional protection against malaria when compared to standard pyrethroid-only nets.

Key messages

Pyrethroid-PBO nets are more effective than standard pyrethroid-only nets in killing mosquitoes and preventing them from blood feeding in areas where the mosquito populations are very resistant to pyrethroid insecticides (high-certainty evidence). Pyrethroid-PBO nets probably reduce the number of malaria infections (moderate-certainty evidence), although further high-quality studies measuring clinical outcomes are needed.

What was studied in the review?

We included 15 trials conducted between 2010 to 2018 that compared standard pyrethroid nets to pyrethroid-PBO nets. These consisted of two laboratory trials, eight experimental hut trials that measured the impact of the pyrethroid-PBO nets on a wild population of mosquitoes, and five village trials. Only one village trial measured the impact of pyrethroid-PBO nets on malaria infection in humans; all other studies recorded the impact on mosquito populations. We analysed all studies to determine whether the pyrethroid-PBO nets were better at killing mosquitoes and preventing them from blood feeding. For the single clinical trial, we examined whether pyrethroid-PBO nets reduced the number of malaria infections. As the benefit of adding PBO to nets is likely to depend on the level of pyrethroid resistance in the mosquito population, we performed separate analyses for studies conducted in areas of high-, medium-, and low-levels of pyrethroid resistance.

What are the main results of the review?

Where mosquitoes show high levels of resistance to pyrethroids, pyrethroid-PBO nets perform better than standard pyrethroid-only nets at killing mosquitoes and preventing them from blood feeding. As expected, this effect is not seen in areas where the mosquitoes show low or no resistance to the pyrethroid-only insecticides. Only one trial looked at the impact of using pyrethroid-PBO nets on the number of people infected with the malaria parasite. This trial, involving 3966 participants and conducted in an area where mosquitoes are very resistant to pyrethroids, found that fewer people were infected with malaria when the population used pyrethroid-PBO nets compared to standard pyrethroid-only nets.

How up to date is this review?

We searched for studies that had been published up to 24 August 2018.