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Effectiveness and efficacy of long-lasting insecticidal nets for malaria control in Africa: Systematic review and meta-analysis of randomized controlled trials

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**Introduction/Problem/Context**

Malaria, a parasitic disease that is transmitted by the bite of a female Anopheles mosquito, can also be contracted through exposure to infected blood products or congenitally. Long-lasting insecticidal nets have significantly reduced the malaria burden in the past decade and this malaria prevalence reduction has been achieved through the upgrading of pyrethroid long-lasting insecticidal nets (LLINs), but the reduction has stopped due to pyrethroid fast resistance. The World Health Organization (WHO) recommends new LLINs with two active ingredients for areas with malaria vectors resistant to pyrethroids. Malaria control in Africa faces threat from pyrethroid resistance, prompting the development of new long-lasting insecticidal nets (LLINs) with dual active ingredients to interrupt transmission in pyrethroid-resistant areas. A study aimed to evaluate the effectiveness and efficacy of different mixtures of active-ingredient LLINs compared to standard pyrethroid LLINs against pyrethroid-resistant malaria vectors showed no reduction in the density of Mansonia spp. in the pyrethroid pyriproxyfen LLIN arm outdoors. Therefore, the objective of this systematic review and meta-analysis is to pool estimates of the effectiveness and efficacy of pyriproxyfen, chlorfenapyr, and piperonyl butoxide long-lasting insecticidal nets (LLINs) with pyrethroid-only LLINs for malaria control in African.

**Method and Materials/procedures**

The protocol was registered in PROSPERO with the protocol number: CRD42024499800. This review used Cochrane methodology to assess risk of bias and evaluate evidence quality. It included cluster randomized or prospective clinical trials comparing long-lasting insecticidal nets (LLINs) of Pyriproxyfen, Chlorfenapyr, and/or Piperonyl Butoxide for malaria control (test arm) and pyrethroid-only standard LLINs (control arm) for malaria control. Three reviewers independently read each preprint or publication and extracted relevant data from individual studies. The search was conducted from 2000 to 2024, and meta-analysis was performed using Excel and STATA 17. The extracted data from eligible studies were pooled using the random effects model and expressed as a risk ratio (RR) with a 95% confidence interval (CI).

**Results** and **Policy Implications**

A total of 11 cluster randomized controlled trials with 21,916 households, 1,145,035 people, and 34,327 children across all of the studies reporting sample size. This study found that the pooled prevalence of post-intervention malaria infection among children using chlorfenapyr, piperonyl butoxide, and pyriproxyfen long-lasting insecticidal nets was 25.58 per 100 children, 32.38 per 100 children, and 33.70 per 100 children, respectively, compared to the control group/pyrethroid-only long-lasting insecticidal nets of 40.84% per 100 children in Africa, which is higher in the control group.

The study found that the post-intervention pooled mean indoor vector density per household per night in the control group/pyrethroid-only long-lasting insecticidal nets was higher than in the intervention groups, with pyrethroid-only nets having the highest density at 8.04 per household per night, compared to other insecticidal nets (7.74 per 100 households in pyriproxyfen, 5.53 per 100 households in chlorfenapyr, and the lowest 1.9 per 100 households per night in piperonyl butoxide) in Africa.

The study determined that the post-intervention pooled sporozoite rate per mosquito in the control group/pyrethroid-only long-lasting insecticidal nets was almost two to three times higher than in the intervention groups, with pyrethroid-only nets having the highest sporozoite rate per mosquito at 227 per 100 anopheles, compared to other interventional long-lasting insecticidal nets (165 per 100 anopheles in pyriproxyfen, 172 per 100 anopheles in piperonyl butoxide, and the lowest 79 per 100 anopheles in chlorfenapyr) in Africa.

A meta-analysis found that pyriproxyfen (PPF) long-lasting insecticidal nets (LLINs) effectively reduce indoor vector density by 1%, entomological inoculation rate by 7%, and sporozoite rate of malaria parasites by 15% compared to pyrethroid-only LLINs in Africa, despite no significant difference in malaria infection, case incidence, and anemia reduction among children.

The study found that piperonyl butoxide (PBO) long-lasting insecticidal nets (LLINs) are highly effective and efficacious in reducing malaria infection by 1%, case incidence by 2%, and anaemia by 3% among children, as well as reducing indoor vector density by 3%, the mean entomological inoculation rate by 12%, and the sporozoite rate by 10% in Africa as compared to pyrethroid-only LLINs in Africa.

The study found that chlorfenapyr (CFP) long-lasting insecticidal nets (LLINs) are highly effective and efficacious in reducing malaria infection by 1%, case incidence by 1%, and anaemia by 4% among children, as well as reducing indoor vector density by 4%, the inoculation rate by 23%, and the sporozoite rate by 9% in Africa as compared to pyrethroid-only LLINs in Africa.

The study compared the effectiveness and efficacy of chlorfenapyr (CFP) and pyriproxyfen long-lasting insecticidal nets in Africa. Results showed that CFP nets were highly effective, and efficacious in reducing malaria infection, case incidence, indoor vector density, inoculation rate, and sporozoite rate by 1%, 15%, and 7%, compared to pyriproxyfen nets long-lasting insecticidal nets for malaria control in Africa.

The evidence evaluating the effectiveness and efficacy of piperonyl butoxide (PBO) compared with pyriproxyfen long-lasting insecticidal nets found that piperonyl butoxide (PBO) long-lasting insecticidal nets (LLINs) are highly effective and efficacious in reducing malaria infection by 0.0%, case incidence by 2% among children, indoor vector density by 4%, inoculation rate by 5%, and sporozoite rate by 1% in piperonyl butoxide (PBO) as compared to pyriproxyfen long-lasting insecticidal nets for malaria control in Africa. Critical appraisal of individual randomized control trials revealed that 100% of the studies scored high quality, and Cochrane methodology was used to assess the risk of bias and evaluate evidence quality, which was graded as high. This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different is low.

This generated evidence was evaluated the effectiveness and efficacy of pyriproxyfen, chlorfenapyr, and piperonyl butoxide long-lasting insecticidal nets against the pyrethroid-only LLINs.

This study found that PYR-only LLINs (control arm) had higher pooled prevalence of malaria infection, case incidence, anaemia, mean indoor vector density, inoculationrate, and sporozoite rate as compared to intervention group (PPF, CFP, and PBO LLINs

**Conclusion**

The evidence generated from this meta-analysis reveals that pyriproxyfen (PPF) long-lasting insecticidal nets (LLINs) have no significant difference in malaria infection, case incidence, or anemia reduction among children as compared to pyrethroid-only LLINs. However, this study found that Pyriproxyfen (PPF) LLINs effectively and efficaciously reduce indoor vector density, entomological inoculationrate, and sporozoite rate of malaria parasites compared to pyrethroid-only LLINs.

The study found that chlorfenapyr (CFP) and piperonyl butoxide (PBO) long-lasting insecticidal nets (LLINs) are highly effective and efficacious in reducing malaria infection, case incidence, and anaemia among children, as well as reducing indoor vector density, inoculation rate, and sporozoite rate in Africa as compared to pyrethroid-only LLINs.

The evidence generated found that piperonyl butoxide (PBO) long-lasting insecticidal nets effectively and efficaciously reduce indoor vector density, entomological inoculation rate, and sporozoite rate of malaria parasites compared to Pyriproxyfen (PPF) LLINs, but no significant difference was found in malaria infection reduction among children who use piperonyl butoxide (PBO) versus Pyriproxyfen (PPF) long-lasting insecticidal nets in Africa.

The study found that chlorfenapyr (CFP) long-lasting insecticidal nets (LLINs) are highly effective and superiorly efficacious in reducing malaria infection, case incidence, and anemia among children, as well as reducing mean indoor vector density, mean entomological inoculation rate, and sporozoite rate compared to pyriproxyfen (PPF) long-lasting insecticidal nets (LLINs) in Africa. Therefore, policymakers and health planners should give a great deal of emphasis on addressing the effectiveness, efficacy, and resistance management of long-lasting insecticidal nets (LLINs) as part of their current public health agenda to eliminate malaria.