



Conditions for deployment of mosquito nets treated with a pyrethroid and piperonyl butoxide

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RECOMMENDATIONS

BACKGROUND

Mosquito nets that include both a pyrethroid insecticide and the synergist piperonyl butoxide (PBO) have become available. PBO is a synergist that acts by inhibiting certain metabolic enzymes (e.g., mixed-function oxidases) within the mosquito that detoxify or sequester insecticides before they can have a toxic effect on the mosquito. Therefore, compared to a pyrethroid-only net, a pyrethroid-PBO net should, in theory, have an increased killing effect on malaria vectors that express such resistance mechanisms. However, the entomological and epidemiological impact of pyrethroid-PBO nets may vary depending on the bioavailability and retention of PBO in the net, and on the design of the net (i.e., whether only some or all panels are treated with PBO).

Five pyrethroid-PBO net products have been evaluated under the WHO Pesticide Evaluation Scheme (WHOPES) to determine whether they meet the criteria established for classification as a pyrethroid-treated long-lasting insecticidal net (LLIN).¹ WHOPES evaluation focused on assessing the physical durability of the net, and the biological activity and wash-resistance of the pyrethroid but not the PBO treatment. All five pyrethroid-PBO nets underwent experimental hut² evaluations, and two are currently undergoing long-term field evaluations.³

In accordance with the revised WHO evaluation process for vector control products, current WHOPES recommendations for the five products⁴ are being converted into a WHO prequalification listing.⁵ In line with the evaluations undertaken, the WHO recommendation for these products has been as pyrethroid-only LLINs. In 2014, the WHO Vector Control Advisory Group (VCAG) also reviewed one of the pyrethroid-PBO nets (PermaNet[®] 3.0)⁶ for a claim of increased efficacy against malaria vectors with cytochrome P450-based metabolic pyrethroid resistance. The public health value⁷ of PermaNet[®] 3.0 against vectors with cytochrome P450-based metabolic pyrethroid resistance, however, could not be established due to insufficient epidemiological data.

In 2015, WHO's Global Malaria Programme (GMP) convened an Evidence Review Group (ERG) to define the conditions for use of pyrethroid-PBO nets. WHO released an initial set of recommendations in December 2015. Since the 2015 ERG, a randomized controlled trial in the United Republic of Tanzania has generated new epidemiological evidence for pyrethroid-PBO nets. As a result, the WHO/GMP ERG re-convened in June 2017 to assess whether these new data demonstrate the public health value of pyrethroid-PBO nets in terms of the control of malaria where vectors are pyrethroid-resistant. Details of the review process, quality of the evidence, outstanding questions, and proposals to further strengthen the current evidence can be found in the ERG meeting report, which will be made available upon publication of the randomized control trial data.⁸

In the ongoing transition of the WHO evaluation process for vector control products from WHOPES to the Prequalification Team, WHO has developed an updated policy recommendation on pyrethroid-PBO nets that takes into account the epidemiological trial data from Tanzania. This update is an attempt to further clarify the available evidence base for these types of nets, their categorization under the revised evaluation system, and the additional data required to support WHO's policy-making process. This represents an exception to the standard review procedure, which requires a minimum of two epidemiological trials to assess the public health value of new vector control tools not covered by an existing WHO policy.

These recommendations replace the 2015 WHO recommendations on pyrethroid-PBO nets and will be further revised as new data become available.

CONCLUSIONS & RECOMMENDATIONS

On the basis of the current evidence, WHO concludes and recommends the following:

1. **Epidemiological data from one cluster randomized controlled trial indicated that a pyrethroid-PBO net product had additional public health value compared to a pyrethroid-only LLIN product in an area where the main malaria vector had confirmed pyrethroid resistance of moderate intensity conferred (at least in part) by monooxygenase-based resistance mechanism as determined by standard procedures.**^{9,10} This conclusion is based on a comparison of malaria infection rates in children in village clusters allocated pyrethroid-PBO nets (Olyset® Plus) and rates in village clusters allocated pyrethroid-only LLINs (Olyset® Net) over a period of 2 years in Muleba, United Republic of Tanzania. Entomological data from experimental hut studies on several similar pyrethroid-PBO products conducted in areas of pyrethroid resistance support the finding that pyrethroid-PBO nets are more effective at killing resistant mosquitoes. Mathematical modelling work drawing on relevant entomological data indicates that the added benefit of pyrethroid-PBO nets compared to pyrethroid-only LLINs is expected to be the greatest where pyrethroid resistance is at "intermediate levels", meaning where mosquito mortality after exposure to a pyrethroid insecticide in WHO test kits or CDC bottle assays ranges from 10% to 80%.¹¹ The benefit of pyrethroid-PBO nets is expected to diminish where bioassay mortality is outside of this range. Pyrethroid-PBO nets are not expected to have any added benefit in areas where the main malaria vectors are susceptible to pyrethroids and/or do not harbor resistance mechanism(s) that are affected by PBO, i.e., monooxygenase-based resistance mechanism.¹⁰

2. **Based on the epidemiological findings and the need to deploy products that are effective against pyrethroid-resistant mosquitoes, pyrethroid-PBO nets are being given a conditional endorsement as a new WHO class of vector control products.** As an exception, this establishment of a class is based on a single epidemiological study instead of two studies, as required by VCAG for the assessment of a new product class.⁵ The endorsement is based on epidemiological evidence of the greater effectiveness of pyrethroid-PBO nets in areas of intermediate level resistance. Full confirmation of the class will require VCAG's assessment of data from a second epidemiological trial. Meanwhile, all pyrethroid-PBO nets that have a WHOPES recommendation or WHO prequalification listing will be considered to be at least as effective as pyrethroid-only LLINs at preventing malaria infections – and possibly more effective in areas with intermediate levels of pyrethroid resistance conferred by a monooxygenase-based resistance mechanism.

3. **National malaria control programmes and their partners should consider the deployment of pyrethroid-PBO nets in areas where the main malaria vector(s) have pyrethroid resistance that is: a) confirmed, b) of intermediate level (as defined above), and c) conferred (at least in part) by a monooxygenase-based resistance mechanism, as determined by standard procedures.**¹⁰ Deployment of pyrethroid-PBO nets must only be considered in situations where coverage with effective vector control (primarily LLINs or indoor residual spraying [IRS]) will not be reduced; the primary goal must remain the achievement and maintenance of universal coverage for all people at risk of malaria.

4. **Further evidence on pyrethroid-PBO nets is required to support the refinement of WHO guidance regarding conditions for the deployment of products in this class:**
 - a. VCAG will review data from the third intervention year of the ongoing randomized control trial in Tanzania once they become available. This will determine whether the higher effectiveness of the pyrethroid-PBO net (compared to a pyrethroid-only LLIN) has continued to be observed over the full period for which an LLIN is expected to retain its biological activity (i.e., a minimum of 3 years). These data will contribute to our understanding of whether the pyrethroid-PBO product under evaluation meets the former WHOPES requirements for an LLIN.

 - b. VCAG will review further epidemiological trial data as soon as they become available, such as from a randomized controlled trial planned in Uganda using two pyrethroid-PBO nets (the same product as is being tested in Tanzania, treated with PBO on all panels, and another pyrethroid-PBO net with only the net roof treated with PBO). These data will provide additional evidence on how pyrethroid-PBO nets perform in another geographical setting and whether there are notable differences in effectiveness between products in this class. If VCAG is able to confirm additional public health value, it will allow the conditional endorsement of pyrethroid-PBO nets to be converted into the full establishment of the class.

 - c. The effectiveness of other pyrethroid-PBO nets in comparison to the product for which data were generated in Tanzania needs to be determined. Evaluation procedures to determine whether other

products in a class perform at least as well as the product(s) for which epidemiological data were generated, and for which a product class has been established, are under development. Comparing the effectiveness of different pyrethroid-PBO nets will be aided by:

- c.i. Identifying appropriate entomological indicators to assess the effectiveness of subsequent products entering an existing product class, given that these products will not be required to generate epidemiological data;
 - c.ii. Conducting comparative experimental hut trials on different pyrethroid-PBO nets to determine the relative effectiveness of different compositions of net (e.g., PBO applied to the roof panel of the net only versus all panels of the net), as well as different formulations including initial PBO treatment dosages and release properties;
 - c.iii. Conducting bioassays using characterized reference strains of insecticide-resistant *Anopheles* mosquito(es) on pyrethroid-PBO nets following a minimum of 2 to 3 years of routine use to determine the bioavailability and chemical retention of PBO over time. Current information suggests that PBO retention rates and wash resistance indices are much lower than for the pyrethroid component of the formulations. Studies should be conducted on the PBO-LLIN product assessed in Tanzania, with comparative studies performed on other products of the same class.
- d. Further investigations (laboratory and field studies) are required to determine if there is an antagonistic effect between PBO and the organophosphate pirimiphos-methyl, which is one insecticide recommended for IRS. To date, limited evidence from laboratory studies and the randomized controlled trial in Tanzania suggests that this is not an operational concern; however, further studies are needed to determine the generalizability of current findings.
 - e. Further research will be required to investigate the relationship between entomological indices and epidemiological outcomes for vector control products in order to determine whether entomological surrogates may be sufficient for assessing the public health value of vector control products not currently covered by a WHO policy recommendation.
 - f. Synergist testing methods need to be validated, including identification of appropriate sub-lethal concentrations for pre-exposure to PBO in CDC bottle assays.
5. **Pyrethroid-PBO nets should not be considered a tool that can effectively manage insecticide resistance in malaria vectors.** It is an urgent task to develop and evaluate LLINs treated with non-pyrethroid insecticides and other innovative vector control tools for use across all settings in order to provide alternatives for use in a comprehensive insecticide-resistance management strategy.

Endnotes

The mention of specific companies or certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

1. Guidelines for laboratory and field testing of long-lasting insecticidal nets. Geneva: World Health Organization; 2013 (http://apps.who.int/iris/bitstream/10665/80270/1/9789241505277_eng.pdf).
2. Phase II WHOPES evaluation
3. Phase III WHOPES evaluation
4. WHO recommended long-lasting insecticidal nets. Geneva: World Health Organization; 2017 (http://who.int/whopes/Long-lasting_insecticidal_nets_June_2017.pdf).
5. The evaluation process for vector control products. Geneva: World Health Organization; 2017 (<http://www.who.int/malaria/publications/atoz/evaluation-process-vector-control-products/>).
6. Second meeting of the Vector Control Advisory Group. Summary report. Geneva: World Health Organization; 2014 (http://apps.who.int/iris/bitstream/10665/137318/1/9789241508025_eng.pdf).
7. Public health value is defined as: proven protective efficacy to reduce or prevent infection and/or disease in humans.
8. Report of the evidence review group to define the conditions of deployment of mosquito nets treated with a pyrethroid and piperonyl butoxide, 26–27 June 2017. Geneva: World Health Organization; 2017. This will only be available when the data from Tanzania have been published.
9. Protopopoff N & Rowland M. Effectiveness of a long-lasting PBO treated insecticidal net and indoor residual spray interventions, separately and together, against malaria transmitted by pyrethroid resistant mosquitoes: A community randomised factorial design trial.(Under final peer review)
10. Test procedures for insecticide resistance monitoring in malaria vector mosquitoes (2nd edition). Geneva: World Health Organization; 2016 (<http://www.who.int/malaria/publications/atoz/9789241511575/>).
11. Intermediate level of resistance classified by epidemiological predictions of pyrethroid-PBO nets on average averting >0.1 clinical cases per person per year over pyrethroid-only LLINs (Churcher TS, Lissenden N, Griffin JT, Worrall E, Ranson H. The impact of pyrethroid resistance on the efficacy and effectiveness of bednets for malaria control in Africa. *Elife*. 2016;5:e16090 [<https://elifesciences.org/articles/16090>]).