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Effectiveness and durability of insecticide mixtures for pyrethroid resistance in sub-Saharan Africa

Pyrethroid (PY) resistance is now rampant in most malaria-endemic countries, threatening to lower the effectiveness of standard long-lasting insecticide nets (LLINs) treated with PY only. Of the 88 countries that reported data on insecticide resistance monitoring to the WHO for the period 2010–2020, nearly all of them confirmed resistance to at least one insecticide in one malaria vector species.[1] The next generation of LLINs that combine a PY with a synergist or another active ingredient promises to preserve the utility of LLINs in malaria prevention. There is evidence that these novel combinations are effective in reducing malaria incidence and achieving required entomological outcomes. Two recent landmark trials in Tanzania[2] and Benin[3] showed superiority of chlorfenapyr plus α cypermethrin compared with α cypermethrin either alone or in combination with other active ingredients. In the two studies, outcomes were reported at 24 months of follow-up. The long-term durability of this protection is critical, especially given that LLIN are intended to last a 3-year cycle in most national distribution cycles before they are replaced.

In *The Lancet Infectious Diseases*, Jacklin F Mosha and colleagues[4] follow up participants to 36 months and provide the results of the final follow-up from their four-arm cluster trial in Tanzania. The four groups in this single-blind study were PY LLIN as the reference, pyripoxyfen-PY, synergist piperonyl butoxide (PBO)-PY mixture, and chlorfenapyr-PY. Study LLIN usage was low, at 1325 (30·7%) of 4310 at 30 months and 1023 (22·3%) of 4587 at 36 months. Malaria infection prevalence in children was lowest, at 261 (22·8%) of 1145 in the chlorfenapyr-PY arm compared to 407 (37·4%) of 1088 in the standard PY LLIN arm, 302 (28·8%) of 1050 in the pyripoxyfen-PY arm, and 338 (32·3%) of 1048 in the PBO-PY arm. Only in the chlorfenapyr-PY arm did the data show a significant protective effect (p=0·006) compared to the standard PY arm, and a sustained efficacy compared to the reference in the 3 years of follow-up.

The results from this trial have significant policy implications. Even before the results of the 36-month follow-up became available, the WHO Vector Control Advisory Group used the results of the 24-month follow-up and those from the Benin trial[3] to make positive recommendations about the field use of chlorfenapyr-PY in areas with PY resistance. The results at 36 months strengthen the recommendations of WHO in March, 2023 on the use of chlorfenapyr-PY versus PY-only LLINs in areas with PY resistance. However, WHO placed conditional recommendations on the use of pyripoxyfen-PY versus PY alone based on the poor cost-effectiveness of pyripoxyfen-PY, and on the use of chlorfenapyr-PY versus PBO-PY based on the side effects of PBO-PY. Chlorfenapyr acts through disruption of the oxidative phosphorylation in the mitochondria,

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Published **Online** September 27, 2023 https://doi.org/10.1016/S1473-3099(23)00437-1

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rather than through the neural receptors, and also carries the advantage of no cross-resistance to PYs and other insecticides.[5] However, chlorfenapyr resistance has been detected in non-mosquito populations[6] and could spread widely.

An important lesson from this trial, and others testing combined active ingredients for LLINs, is that more novel products need to be developed and tested. For instance, the LLINs with PBO-PY were protective up to 18 months only; however, in studies elsewhere, the protection lasted up to 2 or 3 years.[7,8] The decline and difference in protection elsewhere compared with the current trial has been attributed by the authors to many reasons, including differences in vector species, chemical specificity, and durability of the textile. The deployment of LLINs in malaria-endemic countries with PY resistance will be smoother if local programmes do not need to consider varying local factors, such as vector species, in order to make choices on the active ingredients in the LLINs to purchase.

Another important lesson from this trial is that malaria control programmes may need to rethink the 3-year cycle for distribution of LLINs. First, the study LLIN usage was very low at 22·3% at 3 years. Use of non-study-related nets was high, probably because the study nets were torn and required replacement. Second, chemical analysis showed the partner active ingredients were very low, at 8% for chlorfenapyr and 7% for PBO. It is, therefore, likely that the overall impact at 36 months was underestimated. The above factors constitute some important weaknesses, which the authors have acknowledged.

This trial has deservedly informed WHO recommendations on the use of active ingredients in LLINs for vector control in areas with PY resistance. However, more trials are needed to replicate and strengthen the basis of the current and future recommendations for malaria vector control.

We declare no competing interests.

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Achieving zero deaths from dengue virus under evolving population immunity

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Published **Online** November 15, 2023 https://doi.org/10.1016/S1473-3099(23)00691-6

As part of its 2021–2030 sustainable development goals, WHO is targeting zero deaths from dengue virus, an arbovirus that circulates throughout subtropical countries.[1] Although health-care access and clinical management are certainly crucial to health outcomes, I argue that, for many countries, the changing epidemiology of dengue virus is resulting in inherent increases in infection–fatality ratios, complicating our ability to achieve this goal.

Currently, around 40 000 individuals worldwide are estimated to lose their lives each year from the virus.[2] In 2023, more than 1000 deaths from dengue virus were reported in Bangladesh alone, a country that historically has been relatively spared from the virus.[3] As with many infectious diseases, the probability of death is strongly influenced by age, with the highest infection fatality occurring in the oldest people. Case fatality from dengue virus in Bangladesh in 2023 increased in a near perfect