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Accelerating the evidence for new classes of long-lasting insecticide-treated nets

The comment by Gerry F Killeen and Hilary Ranson (April 21, p 1551),¹ on our trial of long-lasting synergist piperonyl butoxide and pyrethroid-treated nets and indoor residual spraying for control of insecticide-resistant malaria mosquitoes (April 21, p 1577),² although summarising accurately the trial's findings, was less a commentary on its implications for future malaria control than a critique on the slow rate of progress in getting piperonyl butoxide synergist and other new longlasting insecticidal nets implemented to scale. The appeal by Killeen and Ranson, to roll out interventions not yet tested against malaria outcomes rather than accelerating the evidence based process that our trial intended to inspire, runs the risk of reversing the process of evaluation or resuming the stalemate or free-for-all that arises between products when interventions are not fully assessed. What our study has shown is the importance of rigorous controlled trials to build evidence and guide strategy. What future trials of next generation longlasting insecticidal nets will require is a funding stream that will address the need for more timely evidence on effectiveness and durability. To guide malaria control strategy, an alliance or body of stakeholder representatives should be established that is competent to make far-reaching public health decisions on the basis of that evidence. What would be helpful now is a review of why the stalemate on the use of piperonyl butoxide synergist longlasting insecticidal nets has existed for so long and how this trial can provide lessons for the future.

The authors of the comment took the opportunity to express frustration at the delays in decision making at WHO. With the benefit of the new evidence on piperonyl butoxide treated long-lasting insecticidal nets, it becomes easier to see why policy should change. But, until our trial, there was no definitive evidence that malaria control was being compromised by increasing insecticide resistance or that standard long-lasting insecticidal nets were starting to fail in some places. The global malaria burden had continued to decrease each year in parallel with increasing coverage of standard pyrethroid-treated long-lasting insecticidal nets. What our trial has shown is that resistance is now a substantial problem, standard pyrethroid treated long-lasting insecticidal nets are becoming less effective than before, and alternative long-lasting insecticidal nets containing synergist piperonyl butoxide will provide better protection and transmission control than standard long-lasting insecticidal nets. Before our trial and this year's World Malaria Report,³ which showed that malaria levels had plateaued, there was not enough evidence to justify the switch. Killeen and Ranson say that trials should have been done earlier and, on this, we concur. They call for more trials. We agree with this, too. Before 2017, when WHO adopted new procedures for advising on trials and trial design,⁴ there had been little encouragement from WHO for comparative trials between different classes of long-lasting insecticidal net products on disease outcomes, and no appetite for trials from product manufacturers and funding agencies. Killeen and Ranson say that our findings accord with the less rigorous phase 1 and phase 2 entomological studies that preceded them. They do accord but, until our trial, there was no certainty that they would do so. That the outcomes did broadly accord is reassuring, and we can build on that. Before then, the evidence based on entomology alone was insufficient to shift policy to more expensive piperonyl butoxide treated long-lasting insecticidal nets. The trial did reveal several important findings that were not predicted. We expected an additive effect between the piperonyl butoxide-treated long-lasting insecticidal nets and indoor residual spraying interventions. That we did not see one was surprising, and useful, as it means there is no case for the more expensive combined intervention, when one intervention is sufficient. Killeen and Ranson say that we shall never know whether piperonyl

butoxide-treated long-lasting insecticidal nets could slow the emergence of insecticide resistance. There is plenty of time to show that resistance selection can be slowed down, or even reversed, if the piperonyl butoxide-treated long-lasting insecticidal nets are scaled up fast enough. There are signs that the scaleup is already starting, following on from trial evidence. Another result that might have gone the other way was the effect of pirimiphos methyl indoor residual spraying when combined with standard long-lasting insecticidal nets. Many trials of combinations of indoor residual spraying and longlasting insecticidal nets have not seen an added effect with other classes of indoor spraying insecticides.⁵ The long residual effect of this particular indoor residual spraying is remarkable and unprecedented for any member of the organophosphate or carbamate insecticide class and makes intermittent application of indoor residual spraying a viable malaria control strategy.

The appetite for running a small series of controlled trials on new classes of long-lasting insecticidal nets has recently grown, with the UNITAID Catalytic Fund stepping in to fill the evidence gap identified by WHO. Running in parallel to this series will be a restricted number of pilot rollouts in selected countries to gain more evidence from routine deployment, so that scale-up of the new long-lasting insecticidal nets is not delayed for longer than necessary.⁶

We declare no competing interests.

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1 Killeen G F, Ranson H. Insecticide-resistant malaria vectors must be tackled. *Lancet* 2018; 391: 1551–52.

2 Protopopoff N, Mosha JF, Lukole E, 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.

3 WHO. World malaria report 2017. Geneva: World Health Organization, 2017.

4 WHO. Design of epidemiological trials for vector control products, report of a WHO expert advisory group. Geneva: World Health Organization, 2017.

5 Lines J, Kleinschmidt I. Is malaria control better with both treated nets and spraying?. *Lancet* 2015; 385: 1375–77.

6 UNITAID. Catalyzing the market introduction of next-generation, long-lasting insecticidal nets (LLINs). 2017. <https://unitaid.eu/call-forproposal/catalyzing-market-introductionnext-generation-long-lasting-insecticidalnets-llins> (accessed April 26, 2018).