Insecticide-resistant malaria vectors must be tackled

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Vector control with long-lasting insecticidal nets and indoor residual spraying accounts for most of the 1·3 billion fewer malaria cases and 6·8 million fewer malaria-related deaths attributable to declining transmission between 2000 and 2015.[1–3] However, because resistance to pyrethroid insecticides has spread through African malaria vector populations, concerns over maintaining these gains have been widely voiced—but these are frequently disputed.[4] The findings presented by Natacha Protopopoff and colleagues[5] in *The Lancet* provide rigorous, long overdue, new evidence for those working in the field of malaria vector control.

In their four-group cluster-randomised controlled trial in Tanzanian villages, clusters were assigned to standard long-lasting insecticidal nets treated with a pyrethroid insecticide only, long-lasting insecticidal nets treated with both the pyrethroid and a synergist called piperonyl butoxide (PBO), standard long-lasting insecticidal nets plus indoor residual spraying with the organophosphate insecticide pirimiphos-methyl, or a combination of both PBO long-lasting insecticidal nets and indoor residual spraying. While the PBO synergist added to the pyrethroid-containing long-lasting insecticidal nets neutralises metabolic forms of resistance against this widely used insecticide class, the organophosphate used for indoor residual spraying belongs to a completely different insecticide class that local malaria vector mosquitoes remained fully susceptible to. This study by Protopopoff and colleagues[5] shows conclusively that insecticide resistance does undermine the effects of malaria vector control, and that tackling it with insecticides or insecticide combinations to which local vectors remain susceptible improves impact. After 9 months of intervention, malaria infection prevalence was similar and consistently lower among children in clusters receiving PBO long-lasting insecticidal nets (275 [31%] of 883, odds ratio [OR] 0·37, 95% CI 0·21–0·65; p=0·0011), standard long-lasting insecticidal nets plus indoor residual spraying (252 [29%] of 877, 0·33, 0·19–0·55; p<0·0001), and PBO long-lasting insecticidal nets plus indoor residual spraying (256 [26%] of 969, 0·29, 0·17–0·49; p=0·0001) than in clusters receiving standard long-lasting insecticidal nets (515 [55%] of 932). Not only did these PBO long-lasting insecticidal nets achieve effects similar to standard long-lasting insecticidal nets plus indoor residual spraying after 9 months, the effect was sustained after almost 21 months of use (OR 0·40, 95% CI 0·20–0·81; p=0·0122). Crucially, combining PBO long-lasting insecticidal nets with indoor residual spraying yielded little if any incremental effect, and substantial redundancy was detected (OR 2·43, 95% CI 1·19–4·97; p=0·0158); therefore, a clear choice can be made between these options for tackling pyrethroid-resistant, indoor-biting mosquitoes.

PBO long-lasting insecticidal nets are expected to be more expensive than those with a single active ingredient, and no formal cost-effectiveness estimates or comparisons are presented by Protopopoff and colleagues.[5] Nevertheless, although indoor residual spraying with expensive alternatives to pyrethroids is recommended for insecticide resistance management[6] and can improve malaria vector control impact,[5] it has proven too expensive to scale up.[3] So, although the shift to PBO long-lasting insecticidal nets presents a challenge to low-income countries and their public sector funding partners, these products probably represent a more realistic ambition than universal coverage with indoor residual spraying using prohibitive quantities of relatively expensive alternatives to pyrethroids. Also, such a shift would set an invaluable precedent for market entry of further long-lasting insecticidal net products combining two insecticide classes[7] that are currently awaiting WHO prequalification.

While these findings are welcome, it is disappointing that they have only been very cautiously adopted at global policy level thus far.[8] Although far greater investment in rigorous phase 3 studies is needed, these findings from Protopopoff and colleagues[5] are in accordance with those of less rigorous phase 1 and phase 2 studies that preceded them,[8] as well as predictive modelling studies exploring their programmatic implications.[9] It remains unclear whether early roll-out of PBO long-lasting insecticidal nets could have slowed the emergence of pyrethroid-resistant vectors, and it is now too late to rigorously evaluate their potential for doing so. Although rigorous, large-scale evaluations are indispensable, many other forms of evidence and societal considerations are also essential to rational public health decision making.[10,11] Many of the most successful vector control interventions in history were progressively evaluated as they were rolled out on a programmatic basis, without any preceding studies that would be classified as a phase 3 study today.[12] Public health decision-making processes need to be urgently reformed to facilitate far more proactive investments in and recommendations for resistance management products, even when the best evidence available is less than completely conclusive.[4]

The first PBO-pyrethroid long-lasting insecticidal net received interim WHO approval a decade ago. With dual-active long-lasting insecticidal net products expected to enter the market shortly,[7] and precious few new active ingredients for long-lasting insecticidal nets coming through the development pipeline in the years immediately ahead,[4] there is an urgent need to rethink the decision-making process. How many more cycles of insecticide resistance and supplementation or replacement must the community go through? How many more insecticides that cost huge sums of money to develop must be rendered only partially effective or worse? And how many more preventable malaria-related deaths must occur before stakeholders start making sensible decisions fast enough to maximise their effect on both immediate disease burden and long-term resistance evolution trajectories? As a community, we all need to act to accelerate adoption of new products with resistance management potential and support pre-emptive resistance mitigation as a strategic priority,[4] embracing the more proactive, uncertain decision-making processes that will necessitate.

The process by which new products within existing, recommended intervention classes such as long-lasting insecticidal nets and indoor residual spraying receive recommendations from WHO needs to be much more rapid and decisive. Although Protopopoff and colleagues report a landmark study,[5] it also highlights restrictions in the current framework for evidence review and recommendations. These findings should now prompt a more decisive WHO recommendation for widespread adoption of PBO long-lasting insecticidal nets wherever trade-offs against cost and coverage allow. However, they also confirm that many preventable malaria cases and deaths have already occurred. Current policy is too conservative and slow-moving, relying excessively on proof of incremental benefit in terms of epidemiological outcomes. Inevitably, this requirement restricts insecticide resistance management ambitions to reactive mitigation against insecticide resistance only after it has emerged with public health consequences big enough to measure. In cases where the entomological mode of action is clear, widely accepted, and readily measurable (eg, causing direct adult mosquito mortality rather than reductions of fecundity), evidence of incremental epidemiological impact should no longer be required.

If new products are to be adopted fast enough to delay the emergence of insecticide resistance, it is essential that review and recommendation policies take a bolder stance to emphasise pre-emptive action. If we continue waiting until we have all the evidence we need to be absolutely confident in our most important insecticide resistance management decisions, they will always come too late.

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