Getting ahead of insecticide-resistant malaria vector mosquitoes

Published Online January 24, 2023 https://doi.org/10.1016/S0140-6736(23)00102-2

See Articles page 435

In *The Lancet*, Manfred Accrombessi and colleagues[1] report the results of a rigorous cluster-randomised, controlled, superiority trial in Benin, encompassing 54 030 households and 216 289 people, which confirms that the addition of the pyrrole insecticide chlorfenapyr to long-lasting insecticidal nets (LLINs), as a second active ingredient to back up the pyrethroids we have relied upon so heavily for so long, can have invaluable effects on malaria transmission and disease burden. A total of 115 323 LLINs were distributed to 54 030 households and the primary outcome of mean malaria case incidence 24 months after LLIN distribution in a cohort of children aged 6 months to 10 years showed 1·03 cases per child-year (95% CI 0·96–1·09) in the pyrethroid-only LLIN reference group, 0·56 cases per child-year (0·51–0·61) in the chlorfenapyr-pyrethroid LLIN group (hazard ratio [HR] 0·54, 95% CI 0·42–0·70; p<0·0001), and 0·84 cases per child-year (0·78–0·90) in the pyriproxyfen-pyrethroid LLIN group (HR 0·86, 95% CI 0·65–1·14; p=0·28). Together with a similar study in Tanzania by Mosha and colleagues,[2] these findings decisively confirm that dual-ingredient LLINs containing chlorfenapyr can improve on the epidemiological effect of pyrethroid-only nets in contemporary Africa, where resistance to pyrethroids has become ubiquitous[3] over the 15 years since WHO embraced LLIN scale-up to universal coverage targets.[4]

Louise Gubb/Getty Images

Taken together, these two studies[1,2] now satisfy the WHO requirements for evidence that LLINs with two directly lethal insecticides do indeed add public health value, compared with pyrethroid-only LLINs, so that these next-generation LLIN products can now finally be recommended for procurement by national malaria control programmes.[5,6] Now, approximately 5 years after those criteria were formalised and 4 years after the product in question was prequalified, an unreserved recommendation for this product class is urgently needed from WHO. Indeed, harsh lessons must be learned from all the unacceptable dithering about another class of new LLINs, which complemented pyrethroids with the synergist piperonyl butoxide.[7] Policy makers must now act promptly and decisively, so that national malaria control programmes can finally realise the benefits of this new vector control product with immediate effect. At a strategic level, these studies now establish these chlorfenapyr-containing LLINs as first-in-class products, allowing for much faster adoption of nets with similar modes of action but quite different active ingredients, as long as they show equivalent insecticidal efficacy against resistant mosquitoes.[5,6]

This insightful study by Accrombessi and colleagues[1] also reminds policy makers of several strategically important facts about LLINs that seem to have been forgotten over the past decade.[7] First, the insecticides used to treat LLINs really do matter and make an invaluable contribution to overall impact by killing off mosquitoes at population scales.[4,8,9] Second, the exact choice of insecticide matters, so much so that adding a fully effective new insecticide, even on top of a partially effective old agent, can approximately halve malaria disease burden.[1,2] Third, insecticide resistance dramatically attenuates the epidemiological effects of LLINs, causing avoidable malaria infections and deaths that were widely foreseen.[3] Finally, if we continue to manage resistance to new insecticides in the same short-sighted, reactive manner as we have for pyrethroids, neither chlorfenapyr nor any of the forthcoming alternatives will remain fully efficacious for long.[7]

Although it is disheartening that such stark epidemiological evidence for the consequences of

pyrethroid resistance could only be obtained specifically because it was allowed to become so well established,[7] at least it proves decisively just how urgently investments into new insecticides,[1,3] and smarter ways to deploy them,[10,11] are needed. While global policy still enshrines an unsustainable reactive resistance management strategy in the stated conditions for recommendation of new LLIN product classes,[5,6] surely the time has now come for a decisive switch to pre-emptive strategies that allow us to get ahead of resistance against new insecticides before those traits emerge?[7]

Such an overdue shift would realign stewardship practices for public health insecticide with those established decades ago for antimalarial drugs,[7] with huge implications for product development. For example, it would become more important to maximise the diversity of insecticides deployed than to identify any single, purportedly optimal active ingredient to maximise mosquito mortality and epidemiological impact over the short term.[7] Correspondingly, even active ingredients with less impressive incremental effects than chlorfenapyr might well prove invaluable for pre-emptive resistance management within diversified repertoires of complementary insecticide classes.

For example, Accrombessi and colleagues[1] also evaluated another dual-ingredient LLIN product, in which the established pyrethroid class was complemented by an insect growth regulator intended to sterilise adult mosquitoes rather than kill them, thereby preventing resistant survivors from passing on those traits to their offspring. Although the addition of pyriproxyfen might confer only modest immediate incremental effects on malaria burden in robustly endemic settings, it clearly does augment the vector population suppression functions of LLINs,[1,2,12] and might therefore have considerable utility for pre-emptive insecticide resistance management over the long term.[1] In particular, pyriproxyfen might prove useful as a third-line insecticide in future LLIN products with three or more active ingredients.

Overall, this landmark study[1] not only has immediate short-term implications for what bednet products national programmes should be allowed to procure today, so that they can finally respond effectively to well established pyrethroid resistance tomorrow, it also confirms the urgent need for global policy makers to prioritise innovation and pre-emptive insecticide resistance management strategies yesterday.[3,7] The time has come to finally get ahead of insecticide resistance and stay ahead.

We declare no competing interests.

*Gerry F Killeen, Seynabou Sougoufara
gerard.killeen@ucc.ie

School of Biological, Earth, and Environmental Sciences, University College Cork, Cork T23 N73K, Ireland (GFK); Centre for Applied Entomology and Parasitology, School of Life Sciences, Keele University, Keele, UK (SS)

1 Accrombessi M, Cook J, Dangbenon E, et al. Efficacy of pyriproxyfen-pyrethroid long-lasting insecticidal nets (LLINs) and chlorfenapyr-pyrethroid LLINs compared with pyrethroid-only LLINs for malaria control in Benin: a cluster-randomised, superiority trial. *Lancet* 2023; published online Jan 24. https://doi.org/10.1016/S0140-6736(22)02319-4.
2 Mosha JF, Kulkarni MA, Lukole E, et al. Effectiveness and cost-effectiveness against malaria of three types of dual-active-ingredient long-lasting insecticidal nets (LLINs) compared with pyrethroid-only LLINs in Tanzania: a four-arm, cluster-randomised trial. *Lancet* 2022; **399:** 1227–41.
3 Hemingway J, Ranson H, Magill A, et al. Averting a malaria disaster: will insecticide resistance derail malaria control? *Lancet* 2016; **387:** 1785–88.
4 WHO. Insecticide treated mosquito nets: a position statement. Geneva: Global Malaria Programme; World Health Organization, 2007.
5 WHO. Conditions for deployment of mosquito nets treated with a pyrethroid and piperonyl butoxide. Geneva: Global Malaria Programme; World Health Organization, 2017.
6 WHO. WHO guidelines for malaria. Geneva: Global Malaria Programme; World Health Organization, 2022.
7 Killeen GF. Control of malaria vectors and management of insecticide resistance through universal coverage with next-generation insecticide-treated nets. *Lancet* 2020; **395:** 1394–400.
8 Killeen GF, Smith TA, Ferguson HM, et al. Preventing childhood malaria in Africa by protecting adults from mosquitoes with insecticide-treated nets. *PLoS Med* 2007; **4:** e229.
9 Pryce J, Richardson M, Lengeler C. Insecticide-treated nets for preventing malaria. *Cochrane Database Syst Rev* 2018; **11:** CD000363.
10 Murray GPD, Lissenden N, Jones J, et al. Barrier bednets target malaria vectors and expand the range of usable insecticides. *Nat Microbiol* 2020; **5:** 40–47.
11 Msoffe R, Hewitt M, Masalu JP, et al. Participatory development of practical, affordable, insecticide-treated mosquito proofing for a range of housing designs in rural southern Tanzania. *Malar J* 2022; **21:** 318.
12 Tiono AB, Ouédraogo A, Ouattara D, et al. Efficacy of Olyset Duo, a bednet containing pyriproxyfen and permethrin, versus a permethrin-only net against clinical malaria in an area with highly pyrethroid-resistant vectors in rural Burkina Faso: a cluster-randomised controlled trial. *Lancet* 2018; **392:** 569–80.