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Dawn of the PBO-pyrethroid long lasting net – light at last.

Mark Rowland and Natacha Protopopoff

London School of Hygiene & Tropical Medicine, Department of Disease Control, London UK

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Mosquito vector control with long-lasting pyrethroid treated nets (LLIN) and indoor residual spraying of houses accounts for most of the 1.3 billion fewer malaria cases and 6.8 million fewer malaria-related deaths attributable to malaria prevention since the millennium (Bhatt *et al.* 2015; Gething *et al.* 2016; WHO 2017). Concurrent with this progress, resistance to pyrethroid insecticides has spread through African malaria vector populations. Concerns over maintaining these gains in the face of mounting resistance have been often voiced and sometimes disputed (Hemingway *et al.* 2016). Alternative chemicals to supplement pyrethroids which are safe to use on nets have been developed. The first long lasting net to contain an active ingredient other than pyrethroid to be evaluated by the World Health Organisation (the international authority for setting standards) gained approval more than a decade ago (WHOPES 2008). Long-lasting insecticidal nets containing the synergist PBO (piperonyl butoxide) will neutralise metabolic forms of resistance to pyrethroids. Uptake of PBO-pyrethroid LLIN by malaria control agencies has been slow until this year. It is worth examining the reasons why before considering what might be done to improve the situation. The first reason is the global malaria burden has continued to decrease each year in parallel with increasing coverage of standard pyrethroid-only long-lasting nets. There is little impetus to change the policy when the population covered is still increasing and over half of Africans living in malaria endemic areas are sleeping under pyrethroid treated nets. A series of multi-centre community trials conducted in 5 countries across Africa and in Asia concluded only recently that pyrethroid-only LLIN continue to provide partial protection to users against malaria infection (Kleinschmidt 2018).

The second reason is the nature of the evidence. For the last 15 years, the WHO has required only entomological evidence to recommend new LLIN products for public use. This evidence typically comes from small scale studies where volunteers sleep under the candidate net in special huts under controlled conditions in which the proportion of mosquitoes killed by the LLIN can be measured precisely. This approach has served WHO well for comparing and approving new brands of standard pyrethroid LLIN. Under these conditions PBO-pyrethroid LLIN are shown to kill 20-30% more pyrethroid-resistant mosquitoes than a standard pyrethroid-only LLIN. The question which this approach to evaluation fails to resolve is how would the additional mortality generated by PBO-pyrethroid LLIN translate in terms of malaria transmission control. The answer was never clear. Under natural conditions a mosquito might encounter a standard pyrethroid-only LLIN 2-4 times between contracting a malaria parasite infection from someone and living long enough to incubate the infection and transmit it to someone new. A mosquito, even a resistant mosquito, might be repelled, incapacitated or killed by intermittent pyrethroid exposure during that interval. Could this be the reason why standard LLIN may still provide protection? Mathematical transmission modelling would still predict that PBO-pyrethroid LLIN would provide significant additional transmission control over standard LLIN (Churcher *et al.* 2016). The upshot of this uncertainty was stalemate - WHO felt unable to give a definitive recommendation for PBO-pyrethroid LLIN over pyrethroid-only LLIN and international malaria control agencies like the Global Fund and the US President's Malaria Initiative continued to buy cheaper pyrethroid-only LLIN.

While the importance of LLIN as the primary malaria control tool has continued to grow, our standard approach to evaluating LLIN has not been adequate to the task. Something new was needed to force a change. Thirty years ago when insecticide treated nets were a new idea, rigorous community randomised trials with malaria control outcomes were considered necessary to convince malaria control authorities and governments to invest in this new approach (Pryce *et al.* 2018). With the benefit of hindsight, what was missing was evidence from new community randomised trials that PBO-pyrethroid LLIN would give better control of malaria than standard LLIN against pyrethroid-resistant mosquito populations. For statistical reasons, malaria control trials need to be large scale. Even simple two-arm community randomised trial might involve 40 villages and two years of post-intervention malaria monitoring, costing upwards of \$2 million. Pesticide industry was reluctant to foot the bill. Many companies feel it is difficult enough to recuperate development costs or to translate these into profit from sales of nets or pesticide without adding to the risk by funding large scale malaria control trials of uncertain outcome. Two events coincided to end the stalemate. First, a group of UK donors (the Department for International Development, the Medical Research Council, the Wellcome Trust) agreed to fund a large scale trial of PBO-pyrethroid LLIN versus pyrethroid-only LLIN in a highly malaria endemic area of northwest Tanzania to resolve the question. Second, WHO reorganised its policy making and advisory structures and announced in 2017 that henceforth epidemiological evidence for improved disease control impact was required from community randomised controlled trials before the organisation would grant recommendation for any new class of vector control tool (WHOa 2017). PBO-pyrethroid LLIN fell into WHO's definition of a 'new product class' without which it cannot be recommended or sold in significant numbers. By mid-2017, the first results of the PBO-pyrethroid LLIN community randomised trial began to emerge. Malaria infection prevalence among villages that used PBO-pyrethroid LLIN was reduced by 44% compared to villages that used pyrethroid-only LLIN, and this reduction continued through the second year of PBO LLIN use (Protopopoff *et al.* 2018). The evidence for malaria control impact was clear. WHO convened a second meeting of the Evidence Review Group on PBO-pyrethroid LLIN and on the basis of the new evidence a policy was established recommending PBO-pyrethroid LLIN in all areas of pyrethroid resistance mediated by oxidase metabolism (WHO b 2017). In practice, this means much of endemic Africa. In 2018, procurement of PBO LLIN started to gather pace for the first time and the Global Fund (the major funding agency for malaria prevention) is approving orders for PBO-pyrethroid LLIN from national malaria control programmes across Africa.

The community randomised trial of PBO-pyrethroid LLINs brought other issues to fore. While it would be premature to say pyrethroids are at risk of becoming obsolete, their power to control malaria is certainly waning in some areas. The prevalence of malaria infection was over 50% among users of new pyrethroid-only LLIN throughout the two years of use in the Tanzanian trial area. While it is possible the standard LLINs may have prevented a full blown epidemic, infection prevalence of this magnitude falls short of what many would consider to be adequate control. The multi-country trial cited earlier showed continuing evidence of protection among LLIN users versus non-users (Kleinschmidt *et al.* 2018). Pyrethroids may still confer partial protection through repellency or irritability, or the nets may provide protection as a mechanical barrier to host-seeking mosquitoes. Some observers dispute the evidence that pyrethroid LLIN are failing. In practice, the evidence could never be definitive. If randomised controlled trials are the gold standard, a definitive way to show that pyrethroids are ineffective in an area like northwest Tanzania would be a three-arm trial with epidemiological outcomes of groups randomised to standard pyrethroid LLIN versus groups randomised to untreated nets versus groups with no nets at all in order to separate the effects of pyrethroid plus barrier net from untreated barrier net from no barrier at all. As the

latter two groups could receive less protection, the study design would be considered unethical to conduct. We will have to settle for comparative trials of Dual-active LLIN versus pyrethroid-only LLIN and simply park the question of whether pyrethroid-only LLIN no longer provide protection in some places. The point to emphasise is that protection is no longer enough and it is time to move on to the next generations of LLINs.

Others have taken the opportunity to express frustration at the delays in decision making at WHO (Killeen & Ranson 2018). With the benefit of the new evidence on PBO-pyrethroid LLIN, it becomes easier to see why policy should change. But, until the trial, there was no definitive evidence that malaria control was being compromised by increasing insecticide resistance or that standard LLIN were starting to fail in some places. What the trial has shown is that resistance is now a substantial problem, standard pyrethroid-only nets are becoming less effective than before, and PBO-pyrethroid LLIN will provide better protection and transmission control than standard pyrethroid-only LLIN. For the period 2015-2017 the WHO reports that global malaria burden has shown no significant progress and in Africa it has increased slightly (WHO 2018). Could this be due to pyrethroid resistance?

The power of cluster randomised trials and epidemiological evidence to settle entomological uncertainty has become clear. Had the trial of PBO-pyrethroid LLIN and trials of other classes of 'dual-active or mixture LLIN' been done earlier the policy agenda would be more advanced than it is now. We might be discussing an international insecticide resistance management strategy for African vectors or how to integrate the various new types of insecticide mixture LLIN into a malaria control policy for Africa rather than fighting a rear-guard action to maintain malaria control or bring new insecticides to the fore. Several brands of PBO-pyrethroid LLIN have been approved by WHO. These differ in PBO concentration or pyrethroid compound and will vie with each other for a segment of the LLIN market.

The appetite for running a series of controlled trials on new classes of long-lasting insecticidal nets has recently grown, with DFID/MRC/Wellcome-Trust and independently UNITAID/Global-Fund and the Gates Foundation stepping in to fill the evidence gap identified by WHO. These include dual-active LLIN which contain pyriproxifen to inhibit mosquito reproduction (Royal Guard, DCT) and the pyrrole chlorfenapyr as a supplementary adulticide to the pyrethroid (Interceptor G2, BASF). Running in parallel to this series will be a limited number of pilot rollout of dual-active LLIN in selected countries to gain more evidence from routine deployment. Until there is randomised controlled trial evidence for the new classes of dual-active LLIN, their scale-up will be restricted (WHO a 2017). Owing to the technicality of Interceptor G2 having gained WHO interim approval before the new WHO policy on trial evidence came into force, Royal Guard is excluded from the pilot roll outs. In view of the pressing need to define new resistance management and integrated vector control strategies using multiple interventions, this restriction lacks even-handedness and fails to consider that restricted pilot deployment - conducted on larger or longer scale than a randomised controlled trial - might provide valuable evidence on selection, or even reverse selection of resistance, and early insight into future resistance management strategy.

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