

MEDICAL RESEARCH

Malaria parasite tackled in mosquitoes

Insecticides that kill mosquitoes have helped to fight malaria, but insecticide resistance is rising. Treating mosquitoes with drugs that target the disease-causing parasite offers another way of tackling malaria. [SEE LETTER P.XXX](#)

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Any long-term programme for disease control that relies on one type of intervention has a high probability of failure owing to the development of treatment resistance. Efforts to limit malaria by using insecticides to kill female mosquitoes, which transmit the disease-causing *Plasmodium* parasite, are no exception: mosquito resistance to insecticides is on the increase. Writing in *Nature*, Paton *et al.*¹ report a non-insecticidal intervention that stops mosquitoes from transmitting malaria and that might offer a way to reduce the reliance on insecticides alone as a means of malaria prevention.

It is estimated² that mosquito control using bed nets impregnated with long-lasting insecticides called pyrethroids, and indoor insecticide spraying, resulted in 1.3 billion fewer malaria cases and 6 million to 8 million [Should this be 6.8 million see the 1st ar: <https://www.sciencedirect.com/science/article/pii/S0140673618308444?via%3Dihub#bib2>] fewer deaths between 2000 and 2015. However, despite these intensive efforts, a 2018 report³ by the World Health Organization (WHO) states that, between 2015 and 2017, global efforts to reduce the burden of malaria stalled.

The report highlights a funding gap that has resulted in a failure to achieve universal coverage of bed nets, where needed, and an increase in resistance to antimalarial drugs and insecticides. The report mentions the limited data available on insecticide resistance, and states that the impact of pyrethroid resistance on the effectiveness of current pyrethroid-based interventions is poorly understood. Although mentioning that such increasing resistance will probably reduce the efficacy of current interventions, it downplays the potential impact on the use of pyrethroid-treated bed nets, stating that the nets, which have been responsible for approximately 68% of the estimated reduction in malarial transmission since 2000 (ref. 4), continue to be effective. Sadly, this optimism seems misplaced, given the evidence that the increased insecticide resistance is affecting the

level of disease transmission.

Models had already predicted⁵ that insecticide resistance would affect malaria transmission. A type of bed net called a PBO net that contains pyrethroid and piperonyl butoxide,

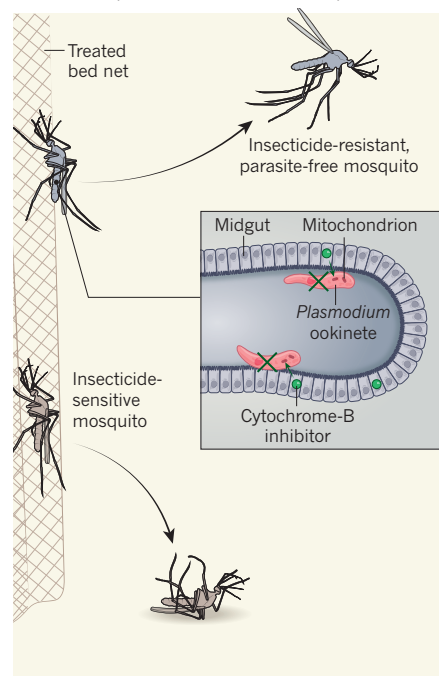


Figure 1 | A non-insecticidal treatment blocks malaria transmission. Transmission of the *Plasmodium* parasite to humans by mosquitoes causes malaria. A standard disease-prevention approach is the treatment of bed nets with insecticides that kill mosquitoes. However, mosquito resistance to insecticides is on the rise. Paton *et al.*¹ report that exposing mosquitoes to surfaces treated with antimalarial drugs targeting the parasite kills the parasite in its host. The authors studied drugs that target the protein cytochrome *b* in mitochondria — the cell's energy-generating organelles. They report that these drugs block the development of ookinete-stage *Plasmodium* parasites in the mosquito midgut. And they suggest that bed-net treatment that combines both insecticides and parasite-targeting compounds might offer a way forward in efforts to develop new ways to tackle malaria. Killing the parasite in this way would prevent insecticide-resistant mosquitoes from transmitting disease.

a compound that enhances pyrethroid's effectiveness, would be substantially more effective than pyrethroid-only nets⁵. Models of transmission dynamics⁵ indicate that even low levels of insecticide resistance would increase the incidence of malaria because of the effect of reduced mosquito mortality and lower overall community protection during the projected three-year lifespan of a bed net. It is estimated that switching from pyrethroid-only bed nets to PBO nets would prevent up to 0.5 clinical cases of malaria per person per year in some scenarios⁵. Trials have demonstrated that PBO nets used in insecticide-resistant areas are more effective at reducing the transmission of malaria than are pyrethroid-only nets⁶.

Given the urgent need to expand the range of effective interventions, Paton *et al.* suggest a way forward for the development of next-generation antimalarial bed nets. They tested whether *Plasmodium falciparum*, the major malaria-causing parasite in Africa, could be killed by exposing mosquitoes to the parasite-killing drugs that are used to prevent people from getting malaria, and which target mitochondria — the parasite's energy-generating organelles.

The authors found that the antimalarial drug atovaquone, which inhibits the mitochondrial protein cytochrome *b*, as well as other types of cytochrome *b* inhibitor drug, could kill parasites in a mosquito host. Exposing mosquitoes for six minutes to a glass surface coated with low doses of the drug was enough to have an effect. This is within the time frame for which wild mosquitoes rest on bed nets. The finding is important because, after more than a century of research, and small-scale projects involving biological or environmental control, it is evident that non-insecticidal interventions do not contribute substantially to efforts to reduce malaria transmission.

Paton and colleagues suggest that antimalarial drugs could be incorporated into bed nets alongside insecticides (Fig. 1). Their modelling predicts that this would reduce the prevalence of malaria, with the size of the impact being affected by the levels of disease transmission, the number of people using nets and the degree of insecticide resistance. The increased effect of adding the antimalarial drug to insecticide-treated nets is most striking in the authors' models when bed-net usage is 70–100%, underscoring the need to strive for high levels of net usage even if the compounds used to treat the nets change in the future.

Malaria cannot be sustainably controlled or eliminated without effective mosquito control. Paton and colleagues' approach fits well with the WHO global plan for managing insecticide resistance⁷. This suggests that a multifaceted approach should be used, and progress will rely on efforts to reduce the cost of bringing

new drugs to market and streamlining the associated development, policy and implementation steps⁸. Although Paton and colleagues' approach holds promise, substantial hurdles must be overcome before a product is generated that is recommended and universally accepted by funders, countries and communities for use in control programmes. Extensive work will be needed to optimize drug development, and so produce long-lasting formulations. Moreover, assessments of the drug-manufacturing process should be undertaken, together with a drug's resistance potential and the cost and public acceptability of the approach.

The WHO has a system called prequalification, in which a product for tackling a health problem must meet certain specifications before it can be placed on a list for selection by donor organizations. In addition, countries

have product-recommendation systems that consider proposed interventions and establish the burden of proof for whether a WHO recommendation is warranted for use there. Completing these steps is a difficult and lengthy process. For example, the first PBO nets were a market-ready product bearing a WHO interim recommendation ten years before the first WHO guidance was issued on where and when this type of net should be used². The combined developmental, regulatory and other processes involved can create a 20-year hiatus before a new technology enters the marketplace and is used at scale. Substantial effort and funding will therefore be needed to ensure a rapid evaluation of whether Paton and colleagues' suggested approach could have a role in reversing the current trend of rising malaria transmission. ■

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Online heading: Battling disease by giving mosquitoes an antimalarial drug