# Antimalarial-treated bed nets could stop parasites developing in mosquitoes

In a fresh approach to blocking transmission of the malaria parasite by mosquitoes, potent antimalarial compounds that kill parasites in mosquitoes are incorporated into bed-net prototypes. Exposure to the compounds through bed-net contact prevents parasite development, even when infection takes place four days later.

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## The problem

Malaria is a leading cause of death globally and kills more than half a million people each year, most of whom are children under five. Insecticide-based control of the mosquitoes that transmit malaria parasites has been one of the most effective tools to combat this disease. Indeed, at the turn of the century, the roll-out of nets treated with long-lasting insecticides helped to avert hundreds of millions of malaria cases[1]. However, their extensive use has led to widespread insecticide resistance that now jeopardizes their continued efficacy and has over the past decade contributed to a plateau in malaria cases and deaths[2]. Tools that capitalize on the preventive efficacy of mosquito control while overcoming the challenge of insecticide resistance are needed to combat this devastating disease. In this study, we develop such a strategy to disrupt parasite transmission by delivering antimalarial drugs to mosquitoes through contact with bed nets[3].

## The discovery

Decades of research have identified diverse antimalarial drugs that effectively inhibit development of the parasite during the portion of its lifecycle that it spends in humans; however, little is known about achieving this in mosquitoes. We screened antimalarial compounds directly in *Anopheles gambiae*, a major mosquito carrier of malaria. We found inhibitors of seven target proteins that are crucial for parasite viability. Exposing mosquitoes that carry *Plasmodium falciparum*, the parasite responsible for more than 90% of human malaria cases, to these inhibitors impaired the parasite's development. We then focused on some of the most-promising hits and studied the relationships between their chemical structure and biological activity to optimize compound uptake by mosquitoes and subsequent antiparasitic activity.

This led to the development of highly potent inhibitors of two sites on a crucial mitochondrial complex of the parasite. When we incorporated these compounds into bed-net-like materials, very low concentrations of the inhibitors killed 100% of parasites, demonstrating their potential efficacy when combined with this commonly used malaria-control tool. The compounds retained their activity even after a year on the net-like substrates and demonstrated long-term activity in mosquitoes, killing parasites even when *Anopheles* females were exposed up to four days before infection (Fig. 1). The compounds were also active in an insecticide-resistant, field-derived line of mosquitoes. We were able to generate these compounds with a simple and high-yield three-step synthesis using inexpensive starting materials, so they could be a viable option for cost-effective malaria control.

## The interpretation

By targeting the parasite directly and specifically during its development in mosquitoes, malaria transmission can be prevented while circumventing the problem of insecticide resistance. The compounds' combination of low synthesis costs and potent antiparasitic activity is a promising indication of their cost-effectiveness; this strategy could be integrated into existing interventions, such as bed nets, to reinvigorate malaria control.

We have yet to test whether incorporating the compounds into insecticide-treated mosquito nets will be effective. We think that antimalarials will be a complementary addition to insecticide-treated bed nets, and an important step will be to confirm that these nets maintain their insecticidal and antiparasitic activity. Encouragingly, for most nets on the market treated with long-lasting insecticides, several active ingredients are used, suggesting that this could be a feasible approach.

A key next step is to partner with collaborators in malaria-endemic regions to move this approach from the laboratory to real-world settings and begin testing with field mosquitoes and parasites. We are already working with our partners in Ethiopia and Burkina Faso to test the level of protection that our bed nets can offer people sleeping under them.

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## EXPERT OPINION

"This impressive body of work moves the prospect of delivering anti-*Plasmodium* drugs through conventional mosquito-control tools a step closer to implementation. The challenges associated with completing such a comprehensive initial screen should not be underestimated. The highlights include the identification of alternatives to drugs already in clinical use and the demonstration of the longevity of activity of some compounds."

**Hilary Ranson** is at the Liverpool School of Tropical Medicine, Liverpool, UK.

## FIGURE

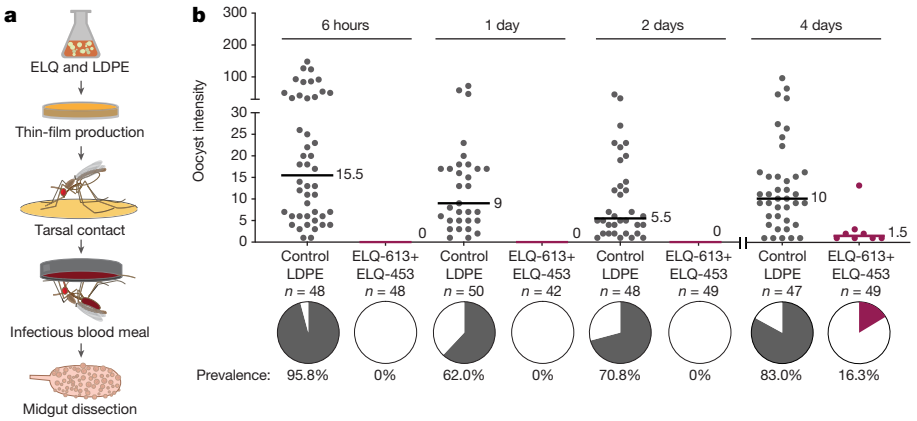


**Figure 1 | Exposing mosquitoes to antimalarial compounds inhibits parasitic development. a**, Optimized antimalarial compounds (ELQ-453 and ELQ-613) were incorporated into low-density polyethylene (LDPE) polymers. Mosquitoes were allowed to land on these polymers for six minutes, mimicking their contact exposure to bed nets, then given an infectious blood meal containing *Plasmodium falciparum*, the parasite that causes most cases of malaria. One week later, mosquitoes were dissected, and the amount of oocysts – an intermediate, growing stage of parasite development in the mosquito – in their midgut was measured. The schematic was adapted from ref. 4, PLOS, under a Creative Commons licence CC BY 4.0. **b**, Brief landing contact with ELQ polymers completely protected mosquitoes from infection for up to two days, and considerably reduced parasite development in mosquitoes even when infection took place four days after exposure to the antimalarial compounds. The midlines represent the medians. Probst, A. S. *et al.*/*Nature* (CC BY 4.0)

## BEHIND THE PAPER

This body of work was the culmination of more than five years of highly collaborative efforts in the community for malaria-drug discovery and development to advance a new transmission-blocking strategy. Key players in academia, industry and non-profit partnerships came together to assemble the compound screening library and support development of promising candidates. As this research advanced, a team of mosquito and parasite biologists and synthetic and polymer chemists worked closely together to develop preliminary net prototypes for real-world applications. The day that we first discovered our compound-incorporated polymers completely blocked parasite development in mosquitoes was not only the exciting fruition of years of effort, but a defining piece of evidence for this strategy as a whole. We are continuing to develop mosquito-targeted antimalarial bed nets and hope that this will ultimately provide another tool to advance malaria-control efforts worldwide.

**A.S.P.**

## REFERENCES

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## FROM THE EDITOR

By demonstrating the feasibility and efficacy of anti-malarial drug uptake via the feet of mosquitoes, this study takes an innovative step forward in malaria control. Killing the parasite inside the insect vector prevents onward transmission and mitigates the use of harmful insecticides. The fact that this novel drug can be stably incorporated into bed net material suggests that it might be scalable and implementable in real-world settings.

**Editorial team**, *Nature*