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VECTOR CONTROL

The last bite

Preventing mosquitoes from transmitting the malaria parasite is a crucial piece of the eradication puzzle.

BY LAUREN GRAVITZ

Mosquitoes are the ideal vector — they provide a safe haven for a parasite to reproduce, then inject it directly into the human bloodstream. What's more, mosquitoes are a moving target. The females of nearly 70 species of *Anopheles* transmit malaria, biting indoors and out. They have evolved resistance to once highly effective pesticides[1], and some species might have even changed their behaviour to bite earlier in the evening when people are less likely to be shielded by bed nets.

To achieve a definitive end to malaria transmission, mosquito populations must be controlled. Some countries with low transmission rates, such as Tunisia and the United Arab Emirates, got rid of malaria using vector control, aggressive treatment and stiff monitoring, but in parts of Africa transmission rates are so high that even reducing bite frequency by 99% would still result in around 10 infectious bites per person per year. In these circumstances, elimination means extraordinary levels of control. "You're talking 99.99% control, which is different from any other pathogen on the planet," says Gerry Killeen, a mosquito biologist and malaria expert who splits his time between the Liverpool School of Tropical Medicine in the United Kingdom and the Ifakara Health Institute in Tanzania. "It makes flu look difficult to transmit."

The last big international push to eradicate malaria, spearheaded by the World Health Organization (WHO), ran from 1955 to 1969 and involved spraying insecticides — primarily the newly developed DDT — on the inside walls of houses[2]. But coverage was inconsistent, high in some countries while low or non-existent in others, and some mosquito populations, such as those that lived in tropical forests, went untouched. This effort managed to eliminate the disease in North America, Europe and parts of Asia, and tamped it down in other regions. Yet by the early 1970s malaria was resurgent on several continents, often reaching epidemic proportions.

The WHO campaign was a massive disappointment — and eradication became known as 'the E word' in some circles. It wasn't until after the successful roll out of insecticide-treated bed nets in the 1990s that governments across the world thought it worth trying again. At first glance, the effort appears to be working: the WHO estimates that it has saved more than a million lives since 2000. But more is needed in order to extinguish the last hotspots of malaria transmission.

HISTORY REPEATING

Many researchers in the field believe that eradicating malaria is possible, but it would require a global strategy that employs a variety of insect-control techniques. "We've seen a vast resurgence of interest and investment in malaria, which is attributable to the advent of the treated net," says Jo Lines, an entomological epidemiologist at the London School of Hygiene and Tropical medicine. As with the 1955 campaign, "The whole business again rests on the effectiveness of the massive scale-up of a single technology."

And once again there are signs of weakness. Lines and others point to insecticide-resistant mosquitoes as a particularly disturbing trend. Pyrethroid insecticides are, by far, the most commonly used pesticide in endemic regions: they're cheap, long-lasting, effective at both repelling and killing mosquitoes, and safe enough that a baby can suck on a pyrethroid-treated bed net without harm. That optimal profile, however, also means that the family of chemicals has been massively overused and is in danger of becoming ineffective.

Similar concerns apply to chemicals besides the pyrethroids. All of the insecticides currently in use for malaria control have come from agriculture; decades of use against bollworms and beetles have had the unintended side effect of exposing mosquitoes to the same chemicals. Now that the mosquitoes are encountering them in people's homes, resistance is spreading. "The frequency with which we hear new reports of insecticide resistance is increasing," says Tom McLean, chief operating officer of the Innovative Vector Control Consortium (IVCC), a UK-based non-profit that partners with companies to pursue novel insecticides. It seems that almost wherever an entomologist looks, he adds, "they find insecticide resistance."

The global health community is working on solutions. In the short term, for example, one aim is to repurpose agricultural pesticides: fast-degrading chemicals for crop use are being reformulated to create longer-lasting insecticides for indoor spraying. Yet these are only stop-gap measures. Many malariologists contend that, in order to maintain progress, they need a larger toolbox.

SPRAY AWAY

Vector control should combine a diverse mix of insecticides for indoor spraying and treating bed nets, a range of repellents — both new and old — and novel ways to decrease population sizes of the worst-offending mosquito species[3]. Researchers are pursuing all strategies.

McLean is optimistic about the outcome of IVCC's projects. "The rate at which we're finding new chemicals suitable for development suggests we'll reach our endpoint by around 2020: a whole new set of insecticides with which we can implement mosaics of vector control," he says.

Matthew Thomas, an entomologist at Pennsylvania State University in University Park, has been working on a different type of insecticide. Rather than synthetic pesticides, he's developing one based on a fungus, with the aim of making it resistance-proof. The fungus, *Beauveria bassiana*,

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TO KILL A MOSQUITO

Various technologies to control malarial mosquitoes are available or are in development

Strategy	Advantages	Disadvantages	Current research aims
Indoor residual spraying	• Deters mosquitoes from entering buildings • Kills mosquitoes that land on walls	• Lasts only 6–12 months • Growing issues of resistance • Needs trained workers • Useless outdoors	• Develop inexpensive and long-lasting insecticides • Develop novel insecticides that act on resistant mosquitoes
Insecticide-treated bed nets	• Deters mosquitoes • Kills mosquitoes that land • Relatively inexpensive	• Last up to 3 years • Growing issues of resistance • Need to be under them indoors	• Investigate long-term • Develop alternative, safe pesticides
Odour-baited insecticide traps	• Reduce outdoor biting	• Can be expensive • Not as useful in rural settings	• Determine most effective structure • Perform cost–benefit analyses
Pesticide applied to water where mosquitoes breed	• Targets species that breed in large, stagnant bodies of water • Hits a different stage of lifecycle, prolonging time to resistance	• Useless against breeding sites in puddles or streams • Must monitor breeding sites • Very expensive and energy intensive	• Develop baited stations and install near breeding pools
Fungus that hobbles and eventually kills mosquitoes	• Works in a different way from current insecticides, so can target resistant mosquitoes	• Not yet field-tested • Only effective in enclosed spaces	• Determine if slow-acting formulations better than fast-acting
Bacterial infection of mosquito to prevent parasite transmission	• Potential long-term control of mosquito populations • Potential to slow transmission of infection	• Requires species-specific *Wolbachia* strains, introduced separately • *Anopheles* proven difficult to infect	• Develop ways to infect the common species • Prove transmission of bacteria through mosquito generations
Genetically engineered mosquitoes	• Long-term control of mosquito populations • Slows transmission of disease	• Sheer number of different species • Widespread fear of genetically modified organisms (GMOs)	• Find most effective mutations • Assess whether GMO would integrate into native populations

starts to work upon contact — the spores attach to a mosquito, penetrate its exoskeleton and burrow inside where they grow, multiply, and produce toxins to fend off an immune attack. The mosquitoes can't fly, eat or smell properly. "It's like a head cold," Thomas says. "Ultimately the insect dies, and how quickly that happens, whether 5 days or 2 weeks, depends on the isolate [fungal strain] we choose."

A faster-acting isolate kills a mosquito before she's old enough to transmit the malaria parasite, which takes 2 weeks to mature. However, the risk is that only the most vulnerable mosquitoes will die whereas more resilient ones will manage to breed and spread resistance. A slower-acting isolate could act as a late-life insecticide: hampering a mosquito's ability to feed and to transmit the parasite yet allowing her to lay some eggs before she dies, thus limiting selective pressure. "We should rethink how we use insecticides," says Thomas. "Not that killing quickly is a bad thing, but it increases speed to resistance." He adds that using the fungal pathogen in combination with other pesticides could further deter resistance by reducing reliance on a single technology.

STEALTH ATTACK

Perhaps the more ambitious of the long-term projects are the ones that aim to change the mosquitoes themselves. Researchers are investigating an assortment of techniques: male sterilization, genetic engineering, even the introduction of bacteria that reduce a mosquito's ability to transmit the malaria parasite. It's an uphill battle — because dozens of different species transmit malaria, scientists will need to separately engineer, breed and distribute each kind of modified mosquito.

The uphill battle, at least for genetic modification, has an army of industry and academic researchers on the case. "There are people doing genomics, bioinformatics, population genetics, protein engineering, computational protein design, germline transformation of mosquitoes, modelling, and working with potential field sites," says Mark Benedict, a molecular biologist and visiting fellow at the University of Perugia in Italy. Benedict is part of an international team that is starting with some conservative modifications — sexually sterile males — and working up to more ambitious plans, such as males that have mostly male offspring. He is developing a strategy to move some of the more promising mosquito strains out of the lab to see if the experimental insects can integrate themselves into natural populations. "The lab experiments are moving very well, very fast. If we had the most powerful, most effective strains in the field in 10 years, I'd be quite happy," he says. But genetically engineered insects have another hurdle to get over: the widespread fear of genetically modified organisms.

Some scientists are trying to circumnavigate that fear by working another angle. Bacteria from the *Wolbachia* genus can infect mosquitoes and decrease parasite transmission. Moreover, the bacteria are transmitted from one generation of mosquitoes to the next, making the infection self-sustaining. *Wolbachia* has been successfully introduced into one mosquito species that transmits another problem disease: dengue. Small trials of the infected vectors in Australia look promising, and show that the bacteria-laden insects quickly integrate into native populations. Within 14 weeks of the release of 250,000 *Wolbachia*-infected mosquitoes, 90% of the populations in the test areas were positive for the bacterium[4].

Such an approach could work for malaria, too. The trick is finding the appropriate *Wolbachia* species — something that has proved very difficult. But entomologist Zhiyong Xi, at Michigan State University in East Lansing, might have found one. He says so far he's managed to introduce the bacterium into one species that's prominent in India and the Middle East and has begun promising efforts with three African species. Xi says he is just beginning talks with India's National Institute of Malaria Research about testing the relevant mosquitoes.

Of course, by the time modified mosquitoes are ready for release, any number of advances could be available, including an anxiously awaited vaccine (see 'The take-home lesson', page S24). Environmental change will also affect the malaria burden. Land development has removed the forests that shelter large mosquito populations. More modern-style houses, with tin roofs instead of mud — ideally with screens on the windows and doors — to prevent mosquitoes from entering in the first place.

The future of mosquito control must ultimately consist of a mixture of current technologies combined with both concentrated science and social development (see 'To kill a mosquito'). Insecticide-treated nets and indoor spraying have helped enormously, "but there's a limit to what they can do," says Killeen. In Tanzania, thanks to these measures, "malaria has crashed down to levels that are normal in other areas. Even at those levels, it's still a major public health problem." ■

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