Efforts to gain control meet resistance

Insecticides Regulatory obstacles stand in the way ofi nnovation, writesSarah Murray

In the field of vector control, as the development of pyrethroids is known, the race is on to come up with new forms before growing resistance to this common form of man-made insecticides reverses recent gains in the battle against malaria.

While promising alternatives are on the horizon, regulatory obstacles threaten to slow the process of putting new insecticides to work.

Pyrethroid insecticides – which are less environmentally harmful and pose a lower threat to non-insect life than products such as DDT – have long been the preferred form of mosquito control. Evidence is emerging that a growing number of mosquitoes are developing resistance to them.

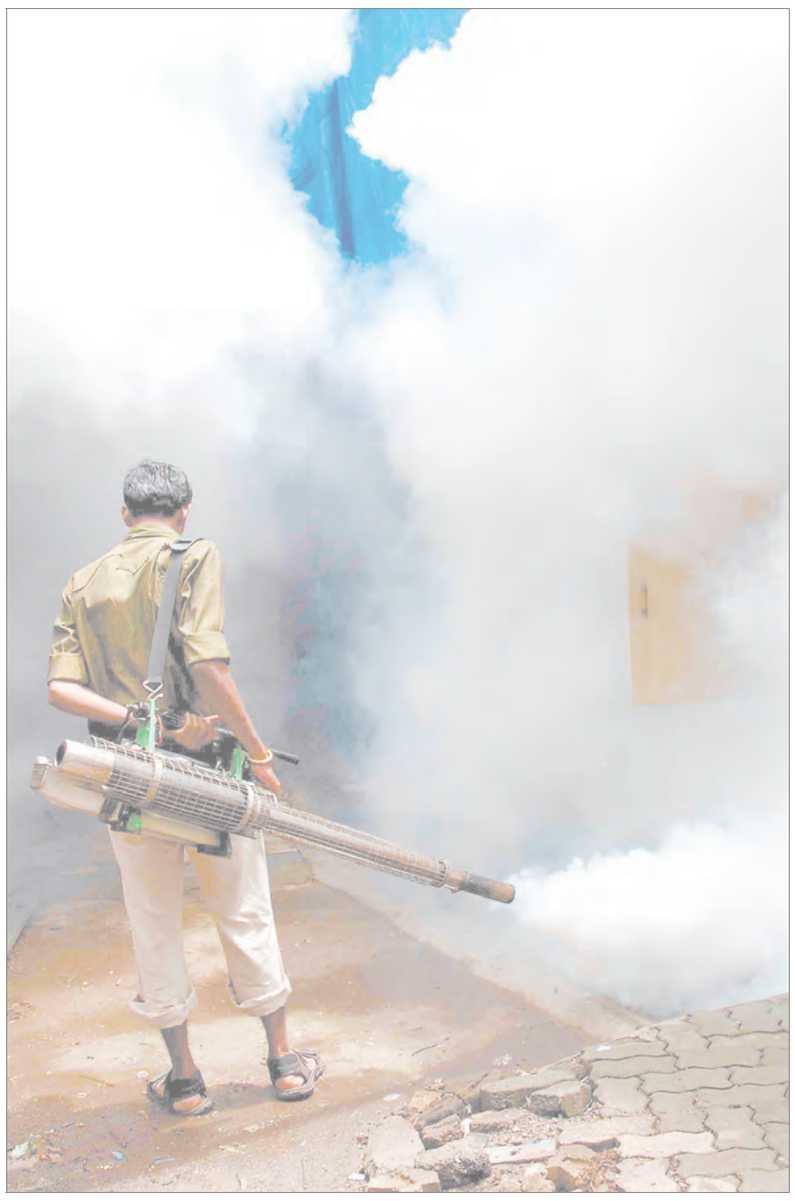
While it is not yet known to what extent this is causing the failure of treated bed nets or indoor wall spraying campaigns, the danger is approaching, says Janet Hemingway, director of the Liverpool School of Tropical Medicine and professor of insect molecular biology. "We cannot assume we're going to have pyrethroids as a viable control tool for much longer," says Prof Hemingway, who is former chief executive of the Vector Control Consortium.

The IVCC, a non-profit collaboration, was launched with $50m from the Bill & Melinda Gates Foundation and is working with the chemical industry to develop new insecticides.

Part of the reason behind the creation of the IVCC was that the flow of innovation in public health insecticides had dried up.

Public health objectives no longer met those of the agrochemical industry, which developed pyrethroids in the 1980s, when what the agriculture industry required "was something that killed everything with six legs and a couple of wings", says Prof Hemingway.

The small size of the market for malaria insecticides and the fact that this market is driven by public funding – with orders dependent on the tender process – has made the business case for the development of new products hard to establish.



A worker in Mumbai, India, administers an antimalarial fumigation spray PA

The IVCC has therefore acted as a catalyst for innovation by providing donor funding to cover early-stage development costs, as well as a skill base companies can tap into.

"It's helping unblock some of the barriers to getting innovation moving," says Mark Birchmore, head of the vector control unit at Syngenta, the Swiss agribusiness group, which is working with the IVCC. "And the IVCC's convening power allows us to have a dialogue that helps shape the innovation portfolio so that we're focusing on the right things."

Because of the length of time needed to develop new insecticides, the approach has been two-pronged. Existing insecticides have been reformulated, with the first, Syngenta's Actellic, going into use last year. Reformulating existing products can fill the gap between increased pyrethroid resistance and the appearance of new insecticides.

"That's quicker to do because the active ingredient is already registered," says Tom McLean, the IVCC's chief operating officer.

Moreover, developing pyrethroid products that incorporate other ingredients can extend their life, since it takes mosquitoes longer to develop resistance to an insecticide that contains a combination of chemicals.

Insecticides with entirely new active ingredients are set to come on to the market in the next five to seven years. However, in addition to the length of time required to develop products, regulation presents additional hurdles.

As well as going through the regulatory approval processes ofi ndividual countries, vector control products are assessed by the World Health Organisation's pesticide evaluation scheme. "That evaluation scheme ends up being a de facto regulatory scheme because at least two of the big donor organisations typically don't allow recipients of aid money to buy products that aren't recommended by the WHO," says Mr Birchmore.

The WHO's four-phase evaluation process can take several years, he explains. "And that's a lot longer than it would take to register a product in the most challenging country from a time point of view."

Mr McLean argues that the WHO's evaluation process can act as a disincentive to companies to develop new products because they are required to invest heavily in demonstrating that a product is safe and effective and then must make that data publicly available.

"It produces a barrier to innovation among industry partners that's severe at the moment," he says. "There are a number of companies saying they will not bring new products through until this is sorted out."

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The IVCC is exploring mechanisms – such as periods of exclusivity or payment of premiums for innovators – that could provide greater incentives for companies to participate in the development of new insecticides.

"We have to draw a reasonable balance between rewarding companies for creating the innovative products that we need without creating monopolies that are then unduly exploited," he says.

"But this problem has been solved elsewhere and the solutions could be applied in this case."

Chance discovery Unintended consequence of drug highlights potential benefits ofi ntegration with other 'neglected tropical disease' programmes

When Moses Bockarie was conducting fieldwork in Papua New Guinea in the 1990s, he noticed a striking side effect when he decided he would take ivermectin, the medicine he was giving to local people to protect them against lymphatic filariasis (elephantiasis), writes Andrew Jack . Mosquitoes that bit him in the laboratory died rapidly afterwards.

The chance discovery added a new and more positive twist to a concern that animal researchers had identified a decade earlier when examining an unintended consequence of using the drug on cattle. Their dung did not decompose because the impregnated faeces killed the flies that usually swarmed around it.

It highlighted a broader message that is even more relevant and useful today. Tighter integration of malaria programmes with other still more "neglected tropical diseases" can provide mutual benefit and offer more effective protection against a range of different debilitating illnesses.

"Ivermectin to kill mosquitoes has become a hot topic," says Prof Bockarie, director of the Centre for Neglected Tropical Diseases at the Liverpool School of Tropical Medicine, who has noticed a surge of recent publications on the matter. While ivermectin's toxicity may be short lived and its potency in different types of mosquito vary, its impact is spreading with growing "mass drug administration" programmes in Africa to tackle lymphatic filariasis and onchocerciasis (river blindness).

Even when it no longer proves lethal, residual levels in the blood may be enough to disrupt the parasite. Ivermectin is a well-studied and well-tolerated medicine.

In a number of African countries ivermectin is now distributed twice a year – albeit often in the dry season when transport is easier.

Timing its use, however, with the peak malaria biting period could help reduce the burden of the three diseases simultaneously – as well as that of scabies.

That is not the only advantage of adopting a less "vertical" single disease-focused approach. Long-lasting insecticide impregnated bednets increasingly provided to tackle malaria are also effective in reducing the burden ofl ymphatic filarasis. Nonetheless, Mr Bockarie says many organisations contracted to provide nets to fight malaria would do well to talk with longer-standing community drug administrators for lymphatic filariasis and onchocerciasis. "Some groups are really not talking to each other," he says.

A final synergy with malaria comes from another neglected tropical disease: worms. Deworming programmes run in schools in Kenya have allowed researchers to get accurate information from children of the extent to which bednets distributed to their homes are actually being put to use.

Such feedback – which suggests that fewer nets are slept under than are distributed to the public – will prove useful in improving coverage and the accompanying education efforts to boost use. With money increasingly tight, cross fertilisation between disease networks could prove ever more a necessity than an unintended bonus.