Preserving pyrethroids

Insecticide resistance threatens to reverse recent gains in malaria control, but new products may soon be available. Patrick Adams reports from Malawi.

Few places could be more conducive to malaria transmission than the Chikwawa district of southern Malawi, a flood-prone wedge of lushly forested lowlands located in the country's Lower Shire Valley. In addition, the climate is tropical and the people are plentiful (about 500 000).

The result: year-round transmission of one of the continent's leading killers.

In 2005, the government of Malawi, with support from the US President's Malaria Initiative and the Global Fund to Fight HIV, Tuberculosis and Malaria, stepped up the distribution of insecticide-treated bed nets free of charge through health facilities around the country, starting with highly endemic areas like Chikwawa.

Between 2005 and 2010, coverage of insecticide-treated bed nets increased from roughly 34% of the at-risk population to more than 60%, while mass media campaigns targeted millions of Malawians with information on the correct use of these nets.

Mass deployment of insecticide-treated bed nets in the countries affected by malaria has contributed to recent gains in malaria control. According to the *World malaria report 2013*, the rate of new cases fell by an estimated 29% globally between 2000 and 2012, while the death rate from malaria fell by 42%.

WHO

Anopheles mosquitoes are widespread in sub-Saharan Africa and are responsible for transmitting the *Plasmodium falciparum* parasite, which is the most deadly of the four malaria parasite species that are commonly known to infect humans

Despite the gains, malaria remains the world's deadliest vector-borne disease – in 2012 it caused an estimated 627 000 deaths, mostly in children aged under five years.

Vectors are organisms that transmit pathogens and parasites from one person or animal to another, causing disease in humans. Vector-borne diseases – the theme of World Health Day on 7 April this year – account for 17% of the global burden of infectious diseases.

Indoor residual spraying and long-lasting insecticidal bed nets are the two most important vector control measures that protect humans from the bite of carrier mosquitoes.

But currently only one class of insecticides – pyrethroids – is recommended for use in bed nets, and this has set the stage for intense selection pressure on what has become the mainstay of malaria control.

Pyrethroids are ideal for treating bed nets because they're safe for humans and other mammals, but toxic to mosquitoes. They're also cheap, durable and effective in killing and repelling mosquitoes with low doses but, as recent data from Malawi and elsewhere in Africa indicate, it remains unclear for how long.

Over recent years, insecticide resistance among *Anopheles* mosquitoes has spread rapidly, having been confirmed in 64 countries, according to WHO's *Global plan for insecticide resistance management in malaria vectors*, issued in 2012.

The plan focuses on insecticide resistance, one of the three major challenges for malaria control globally along with funding and drug resistance. It sets out a comprehensive strategy for preserving pyrethroids' efficacy while calling for a new generation of public health insecticides to be made available as soon as possible.

The plan identifies Malawi as one of the latest countries to report a "high frequency" of resistance to pyrethroids.

But, as the situation in Malawi makes clear, addressing the problem is fraught with challenges. One of the big unknowns is the extent to which pyrethroid resistance is hampering efforts to control the spread of malaria.

According to Dr Themba Mzilahowa, a senior entomologist at the Malaria Alert Centre of the Malawi College of Medicine in Blantyre, more data are needed since current evidence does not suggest that malaria control has been adversely affected by insecticide resistance.

"As far as we can tell, the phenotypic resistance here has not directly translated into the failure of the interventions themselves," says Mzilahowa, whose centre does a lot of entomological monitoring work with funding from the US President's Malaria Initiative (PMI).

> "As far as we can tell, the phenotypic resistance here has not directly translated into the failure of the interventions themselves."
>
> *Themba Mzilahowa*

First established in 2001 with funding from the Gates Malaria Partnership, the Malaria Alert Centre collaborates with the US Centers for Disease Control and Prevention (CDC) on, among other things, routine monitoring of insecticide resistance in the country.

Still, says Mzilahowa, the prospect of malaria control failure in the future remains a major concern. In a study published in the journal *PNAS* in November 2012, he and his colleagues at the Liverpool School of Tropical Medicine showed that pyrethroid resistance had "appeared and spread rapidly in Malawian malaria vectors". Within just three years such resistance had reached "the tipping point for resistance selection", i.e. the moment when resistance starts to rise rapidly.

But what to do about it?

People have only recently started asking that question, says Dr Hilary Ranson, a professor of medical entomology at the Liverpool School and an expert on insecticide resistance, adding:

Bull World Health Organ 2014;92:158–159 | doi: http://dx.doi.org/10.2471/BLT.14.020314

"but this is without doubt one of the most important questions facing [those in charge of] malaria control".

In 2011, Ranson founded AvecNet, a collaborative project involving partners in Europe and Africa, to develop and evaluate new ways to control malaria. "We are trying to come up with standardized guidelines to test new products and, in particular, to assess how well they work against insecticide resistance."

New combination insecticide products may soon be available while a new generation of insecticides is in the pipeline.

Also, three bed nets containing a combination of insecticides have been developed by manufacturers as part of the product development partnership, IVCC (formerly the Innovative Vector Control Consortium). IVCC was established in 2005 to develop new insecticides, information systems and other products to combat malaria.

All three nets incorporate a so-called synergist, which improves pyrethroids' potency against mosquitoes. These are currently being evaluated by the World Health Organization (WHO) Pesticide Evaluation Scheme.

Later this year the public–private partnership says it will be taking three new classes of insecticide into full development to produce insecticides for bed nets and indoor spraying in six to eight years' time.

Meanwhile, Mzilahowa and his colleagues at the CDC launched a study last year in southern Malawi to evaluate two new bed nets incorporating a synergist by comparing them to insecticide-treated bed nets that are currently in use.

Synergist-laden nets have been deployed and studied in western Africa, where results have been mixed. This is the first study to evaluate their impact in southern Africa.

> "Our recommendation is that in places where you've distributed nets, you should not spray with pyrethroids."
>
> *Abraham Mnzava*

"We thought Malawi would be an ideal place to conduct a test because of the high levels of resistance in *Anopheles funestus*," says Dr John Gimnig, an entomologist in the CDC's Division of Parasitic Diseases and Malaria, referring to one of the many species of carrier mosquitoes, adding: "and because the mechanism of resistance – metabolic enzymes – is exactly the target for this synergist".

"Most of the available data on these nets is rather mixed. We assume that this is because the resistant populations were not well characterized and that the existing nets were functioning well. One of my concerns is that we really don't have a good way to show that existing nets are not working. Therefore, we have a challenge in showing that a new product is more effective," Gimnig added.

The resistance observed in *Anopheles funestus*, which rose rapidly from undetectable levels in 2007 to high levels in 2012, has undermined the use of residual spraying indoors as well. And here again Malawi's experience illustrates the challenges that continue to vex decision-makers across the continent.

Malawi, among the countries receiving support from PMI, received funding to expand indoor residual spraying from 27 000 households in 2005 to nearly half a million by 2010. With the emergence of pyrethroid resistance, however, the health ministry switched to an organophosphate insecticide, and the increased cost forced PMI to scale back its support for indoor residual spraying to one district before suspending it altogether, according to PMI's Malaria Operational Plan for 2013.

Although the switch to a more expensive insecticide is a difficult pill for many poor countries to swallow, spraying with pyrethroids could be costlier in the long run, says Dr Abraham Mnzava, coordinator of the vector control unit for the WHO's Global Malaria Programme.

"Our recommendation is that in places where you've distributed nets, you should not spray with pyrethroids," he says, explaining that this practice promotes the resistance that undercuts the tool itself. "The rotational use of different classes of insecticides through indoor residual spraying will help preserve pyrethroids."

Pyrethroids are cheap and people have abused them. "WHO warned a few years ago that we need new tools to fight malaria," says Mnzava, "but no one listened because there wasn't much resistance. Now, if you look for it, you can find it." ■

IVCC/Jed Stone

Child under insecticide-treated bed net in a village near Bobo Dioulasso in Burkina Faso (January 2014)