Pesticide resistance must be countered to control insects that serve as disease vectors

**By Janet Hemingway**

Prevention, diagnosis, and treatment of vector-borne diseases such as malaria, leishmaniasis, and dengue fever is a complex problem. Major reductions in transmission require multiple different interventions, including both disease treatment and vector control. This is particularly crucial in the high-transmission areas where conditions are optimal, or when epidemics are triggered. However, insect-control interventions are becoming less effective; development, evaluation, and introduction of new interventions are slow; and there is limited understanding of just how important these interventions are. To sustain and optimize disease control efforts, it will be necessary to develop more informative models that can inform the timely introduction of new control interventions.

Recent impact-modeling studies have highlighted the importance of vector control. Concerted efforts to reduce malaria in Africa in the past two decades have benefited from better diagnosis, new combination drug therapy, and large increases in the use of bed nets treated with pyrethroid insecticides and the use of pyrethroid-based indoor residual spraying (IRS). Using data on the timing and scale of the changes, Bhatt et al. were able to estimate the relative contributions of the different interventions. To the surprise of many, vector control accounted for 81% of the gains (1). Similarly, Le Rutte et al. recently predicted that increasing IRS coverage from 60 to 80% of all households would have a much greater impact on reducing the time taken to eliminate visceral leishmaniasis than halving the time taken to start treatment from 40 to 20 days, although the greatest benefit would come from combining the two interventions (2).

It follows that insect control is crucial to reduce human suffering. However, heavy reliance on any single intervention—whether an insecticide or a drug—will lead to the selection of resistance. The international community has adopted the use of malaria combination drug therapy to slow the selection of drug resistance, but reliance on pyrethroid insecticides alone has exposed them to intense selection. Pyrethroid resistance, almost nonexistent in the major malaria, Zika, and dengue vectors in the 1990s, is now the norm, and the situation is rapidly degenerating.

Pyrethroid resistance is already affecting the IRS efficacy and malaria prevalence in several countries. For example, resurgence of malaria in South Africa coincided with the re-emergence of *Anopheles funestus* after it became resistant to pyrethroids (3). A World Health Organization (WHO)-led multicountry study on the impact of resistance confirmed that pyrethroid IRS was failing in Sudan (4). Resistance of *A. coluzzii* to pyrethroids also triggered an increase in malaria in Bioko Island, Equatorial Guinea in 2015 (5). Efforts to sustain and further reduce child mortality due to malaria will be compromised unless pesticide resistance is addressed (6).

**COUNTERING PESTICIDE RESISTANCE**

The problem of resistance management is multifaceted, with a series of issues that need to be tackled. To sustain the use of bed nets and IRS, new public health insecticides are required. The overreliance on pyrethroids, a class of insecticides first brought to market in the 1970s, is a direct result of the market for public health insecticides being too small and unstable to support new insecticide development. Between 1950 and 1980, public health insecticides were repurposed from agricultural pesticides. More recently, the target product profile for insecticides used on crops switched from rapid-acting, broad-spectrum insecticides to selective poisons ingested by insect pests through eating the plants. These compounds are not suitable as public health insecticides.

This was recognized in 2005 with the formation of the Innovative Vector Control Consortium (IVCC), which rapidly evolved into a product development partnership between industry and academia (7). Funded by philanthropic and government donations, the IVCC sought to improve the longevity of IRS formulations and establish a new pipeline for public health insecticides for both bed nets and IRS. This initiative has been extremely successful, generating new non-pyrethroid and pyrethroid IRS formulations that last 9 to 12 months (8) and engaging with all major agrochemical companies involved in insecticide research and development to generate a robust pipeline of potential new insecticide classes.

The first new IVCC-supported IRS formulations were launched in 2013 (9). Introduction of a new, long-lasting formulation of the organophosphate insecticide pirimiphos-methyl in Ghana triggered a major drop in malaria prevalence. Since then, this IRS formulation has been rolled out in multiple countries where pyrethroid resistance is high, with similar results. Attention has now shifted to reducing the market cost of the new insecticide formulations to control programs. A large Unitaid-funded program aims to give more price and volume certainty for the companies and thereby bring down the unit price (10).

**THE PROBLEM WITH BED NETS**

The big remaining question is what impact pyrethroid resistance will have on bed net effectiveness. Early waves of nervous system knockdown resistance in African *Anopheles* protected insects from 2 to less than 10 times the dose of insecticide that would normally have killed them and had little or no impact on bed net effectiveness (11); this led to complacency. The metabolic insecticide-resistance mechanisms that have evolved since then have led to anecdotal reports that bed nets may be failing, with increasing numbers of live blood-fed female mosquitoes being collected inside treated nets (12).

In contrast to the relatively rapid uptake of new IRS formulations, non-pyrethroid-based bed nets or “second generation” combination nets, treated with a pyrethroid and a second insecticide or synergist, have had a much harder route to market. The major donors, such as the Global Fund, will not procure more expensive nets without a WHO recommendation that they are substantively better than pyrethroid-only nets. To generate the data to demonstrate this impact, large randomized control trials over several years are needed. Such trials are beyond the financial resources of the manufacturers and the capacity of most disease-endemic countries.

Unless we can break this cycle and generate the data needed to assess whether the new generations of nets represent a more effective and sustainable way of preventing malaria, innovation in this area will cease. Eventual major failure of the pyrethroid-treated bed nets will be catastrophic.

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SYNERGISTIC INTERVENTIONS

Ideally, mosquito-borne disease prevention should use multiple synergistic interventions. Integrated vector management (IVM) has been advocated for many years as a means of reducing reliance on chemically based interventions and reducing the selection exerted for resistance from a stand-alone intervention. In principle, this should be the route forward, but in practice disease endemic countries struggle.

Take the case of Malawi, a relatively poor land-locked African country with high perennial transmission of malaria (13). An IVM national plan, endorsed by the major donors President’s Malaria Initiative and Against Malaria Foundation and introduced in 2013, required distribution of one long-lasting insecticidal net (LLIN) per 1.8 population, IRS in 12 of 28 districts, larval-source management, and improved insecticide-resistance monitoring and management. However, detection of pyrethroid resistance in *A. arabiensis* and *A. funestus* in 2010 forced a change to a more expensive insecticide for IRS; only a single district was treated. Lack of local capacity prevented larval-source management and effective insecticide-resistance monitoring and management planning. Malaria cases declined from a peak of 6.75 million in 2010, but by 2015 had rebounded to 1999 levels (14).

Malawi is not alone in facing these issues, and we need to be realistic about what can be implemented operationally. Sri Lanka, where malaria was eradicated in 2016, provides an example of what can be achieved using multiple interventions. Here, sequential use of restricted larviciding early in the transmission season, followed by IRS, dramatically reduced malaria between 1970 to 2000 and paved the way for eradication.

A WAY FORWARD

The top priority must be to ensure that current IRS and LLIN interventions remain viable. New compounds against which no resistance has yet been selected need to be introduced in combinations. Research can inform operational activity, but only if it is made accessible to the end users, for example through translation of key messages into language that can be understood by nonscientists.

Advanced genomic analysis can be used to look at signatures of selection starting to appear in the genomes of mosquito field populations, well before operational resistance becomes an issue, giving time for mitigation strategies to be deployed (15). New insect tracking technologies can be used to refine and optimize product development and placement (16).

For any of these advances to make a difference in disease control, manufacturers of new interventions need clarity on the route, time, and cost to market for products with a public health benefit. The WHO is responsible for normative guidance and product recommendations, without which major donors will not purchase products; development of this guidance involves several different WHO committees and can take up to 10 years and many millions of dollars. To give manufacturers the required clarity, it is crucial that this process becomes more transparent, efficient, and streamlined.

Reliance on insecticides could be reduced through technologies such as genetic manipulation of the insects to block their ability to transmit disease. CRISPR-Cas9 gene editing has the potential to revolutionize our ability to manipulate the insect vector. However, resistance to CRISPR-Cas9 editing can be selected very quickly in population replacement strategies (17). The extreme variability of mosquito genomes suggests that this editing technology will not be simple technically or logistically to roll out effectively.

REFERENCES

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The way forward for vector control
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