# Insecticide Resistance and Malaria

*A Threat Decades in the Making*

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*A Report of the CSIS Global Health Policy Center*

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**William G. Brogdon, Anthony Fiore, S. Patrick Kachur, Laurence Slutsker, and Robert A. Wirtz**[1]

Insecticide (DDT) use to control malaria was first employed successfully in the antimalaria program in Greece in 1947. By 1951, DDT success in controlling malaria was reported in 22 countries. However, that year also saw the first report of DDT resistance, in *Anopheles sacharovi* in Greece. By 1954, resistance to DDT among mosquitos was known to be a global problem, documented in Europe, the Americas, Africa, and Asia. The World Health Organization–led Global Malaria Eradication Program (GMEP) began in 1955, when resistance was already pronounced worldwide. Scientists did not identify the underlying biochemical mechanism contributing to insecticide resistance until 1958. By then, insecticide resistance was recognized by many to be a major contributor to the ultimate dismantling of GMEP, given the limited capabilities and knowledge of the time. Consequently, the global focus shifted from malaria “eradication” to malaria “control” in the late 1960s.

Currently, the world faces a far more serious problem than in 1958: pyrethroid insecticide resistance. Luckily, some decades later, there is much deeper scientific knowledge of resistance, stronger programmatic approaches, and new chemical tools to tackle this problem in spite of its complexities. Key to success in overcoming insecticide resistance is the adoption of a strategic approach: sustained financing, high-level political will, substantial country ownership, and training of a new generation of skilled African entomologists. Prompt, determined, and coordinated action is no less essential.

## The Current Situation

Pyrethroid insecticide resistance is spreading and intensifying, reaching levels that threaten control in most of Africa. However, the map in Figure 1 illustrates clearly that the problem of resistance is most serious in West Africa, where there is resistance to all classes of pesticides. Lack of adequate baseline surveillance data on insecticide efficacy, as well as inadequacies in ongoing surveillance, contribute to the emergence and spread of resistance.

These shortcomings have delayed a coordinated response to emerging resistance. Moreover, programs use a limited number of insecticides during the same timeframe

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on all bed nets or walls; thus mosquitoes have the opportunity to develop resistance to each insecticide in its widespread use. Strategies for resistance management are further hampered by the limited armamentarium of insecticides, affecting both long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS). Bed nets use only a single class of insecticide—the synthetic pyrethroids. For indoor spraying, there are a few more options available that can be used to manage resistance, but these alternatives are considerably more expensive than pyrethroids.

The potential impact of resistance on U.S. investments in vector control is illustrated by data from the President's Malaria Initiative (PMI) in Figure 2. At least 47 percent of PMI resources are invested in indoor spraying and insecticide treated bed nets. Additional substantial resources are allocated for research and surveillance. In Y2013, PMI procured more than 40 million bed nets and sprayed more than five million houses with insecticides.

Comparison of Figures 1 and 3 shows that major gains in child survival have been seen in West Africa, where resistance is an established threat.

Resistance should be identified and mitigated while it still focal (i.e., concentrated within specific localities). Fortunately, resistance still tends to be highly localized, especially where the strength of resistance threatens control programs. This holds true for programs using bed nets or indoor spraying, either individually or in combination.

## Mechanisms of Resistance

Insecticide resistance is a continually moving target that requires constant attention. It is important to understand the causes of insecticide resistance, so as to inform program efforts to mitigate or reverse this threat. There are multiple biochemical and molecular changes (termed mechanisms) that cause resistance within mosquitos. These can be specific to a particular insecticide or class of insecticides, but the most troublesome molecular mechanisms can create cross-resistance between insecticides and insecticide classes. These mechanisms of resistance may act independently or in concert, making it difficult to diagnose the root cause of resistance, and in some instances drastically enhance severity.

## Additional Challenges to Successful Vector Control for Malaria

Weak bed net durability is a problem that can hamper malaria control efforts. It can complicate determining whether reductions in effective malaria control are due to insecticide chemistries or failed bed nets. In some cultures and locations, bed nets are badly deteriorated after a relatively short time (one to two years) of daily use. Physical damage to nets appears the major limitation impacting net effectiveness, rather than any problem with loss of insecticide from the net material. Efforts are underway among manufacturers to strengthen net structure. Also, as gains are made with reduction of indoor transmission of malaria, reductions of outdoor and daytime or early-evening transmission become ever more substantial.

# The Paths Forward

## Enhanced Surveillance for Insecticide Resistance

Most instances of resistance (especially at their onset) occur in isolated locales. This means that enhanced resistance surveillance, particularly of resistance ***intensity*** or strength, can allow for much more tailored and timely responses. Simple bioassay methods (i.e., exposure of field-collected mosquitoes to precisely determined dosages of insecticide) are currently in field tests to assess their ability to measure resistance intensity.

In recent years, biochemical and molecular methods of studying resistance have generated valuable results. Bioassay tests will further improve the detection of resistance hot spots and help guide control programs. Considerable species shifting of mosquitoes from those that feed indoors during the time people are sleeping to those that feed early or outdoors is occurring throughout Africa, adding to the challenge of clearly establishing which mosquito species are becoming or are already resistant and whether the malaria-transmitting mosquitoes are actually being controlled.

Internet databases mapping insecticide resistance reports are also now available. One of the most informative is IR Mapper, produced for the web by Vestergaard-Frandsen. These databases are especially useful when they document resistance "hot spots" within an individual district of a country. The key to enhancing their usefulness is to keep the information as updated as possible.

Increased surveillance requires much greater attention to capacity building in entomology throughout Africa. Fully capable and motivated young African scientists should be recruited, trained, and supported if resistance management is to succeed.

## Aggressive Resistance Management

Universal net-distribution schemes and use of a single insecticide for indoor spraying invite resistance, much like monoculture farming without crop rotation. What begins as focal resistance is allowed to rapidly spread and intensify over wider areas. Control should be executed locally with higher attention to the significant differences in resistance that occur even between and within districts of individual countries. At the same time, vector control should ensure universal protection for populations at risk.

There are promising strategies in the 2012 WHO publication: "Global plan for insecticide resistance management in malaria vectors."[2] However, there are some practical limitations to implementation, as some of the options presented are not feasible on cost grounds. For example, prophylactic rotation of insecticide classes before resistance is detected can be effective but the cost considerations make this strategy difficult to implement. Even after resistance has been detected, switching classes (to what is typically a more expensive insecticide) has forced some programs to terminate or to severely restrict coverage with indoor spraying due to high costs. Therefore it is imperative that resistance management focus on "hot spots," or areas

[2] World Health Organization (WHO), "Global plan for insecticide resistance management in malaria vectors," May 2012, http://www.who.int/malaria/publications/atoz/gpirm/en/.

of high-intensity resistance in order to be cost-effective. Of course, resistance surveillance should be of sufficient quality to support this approach, thus the vital importance of building entomologic capacity in vector-control programs throughout the continent.

Finally, an additional goal of resistance management is to preserve pyrethroid efficacy and seek to restore it if lost. The importance of pyrethroid efficacy is linked to progress in production of new affordable vector-control chemistries and methods. At this point, there are hopeful signs from the field. In particular, pirimiphos methyl has shown considerable effectiveness in selecting against oxidase resistance mechanisms (an important form of metabolic resistance), currently the most threatening form of resistance.

### Affordable New Chemistries and Products

The most optimistic scenario is that new insecticide chemistries should be available for deployment within two to three years, especially for indoor spraying where new formulations of such insecticides as pirimiphos methyl are already making a difference. In addition, new products have also begun to appear for bed nets. Already, some nets are employing a specific inhibitor of resistance-causing oxidases, one of the most threatening mechanisms for pyrethroid resistance within mosquitos.

Manufacturers are also intensively studying the development of combinations of different insecticide classes in the same net or in durable wall linings (DWLs). These combination nets and materials seem likely to become essential tools in resistance management. However, the introduction of new chemistries and materials will likely be accompanied by increased costs. In addition, regulatory barriers could delay development and deployment of innovative approaches.

## Conclusions

Insecticide resistance is a major threat to the success of malaria vector control programs. While a few countries face the threat of widespread resistance, on the whole insecticide resistance tends to be highly localized and unstable, meaning there is still time to act.

Capacity building to support adequate resistance surveillance is a crucial component of any response to this challenge. Early recognition of resistance as highly localized can save considerable time and precious resources. Too often, resistance surveillance is regarded as “operational research”; instead, it should be recognized as a key pillar of malaria programming, as integral as spraying or distribution of bed nets.

Determined efforts are underway around the world to produce new approaches, chemistries, and creative uses of combination products. It is important that the pesticide industry be a partner in the process of resistance management. It is also important to examine the possibilities of accelerating production, including introducing more flexible regulatory standards, while still ensuring safety and efficacy.

Despite the many challenges, insecticide resistance is still at a point where it can be mitigated or even reversed with innovative, strategic interventions. Armed with new knowledge, chemistries, and programs, the world is not fated to repeat the mistakes of the 1960s. Many lives depend on a strategic, and coordinated response. While insecticide resistance once forced a shift in global strategy from eradication to control, tackling this challenge head on can contribute to a growing movement toward elimination.

**Figure 1**

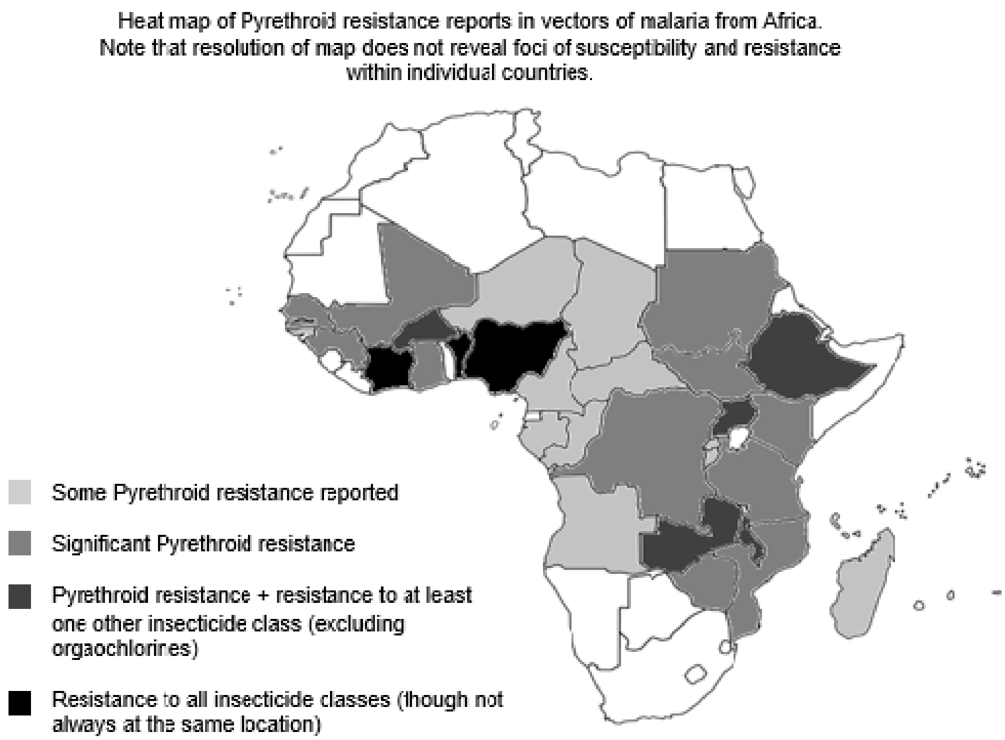
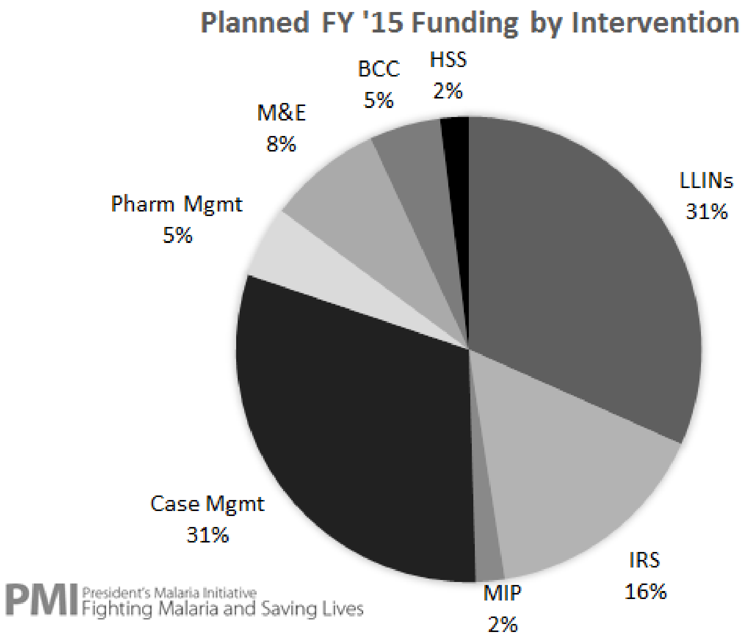
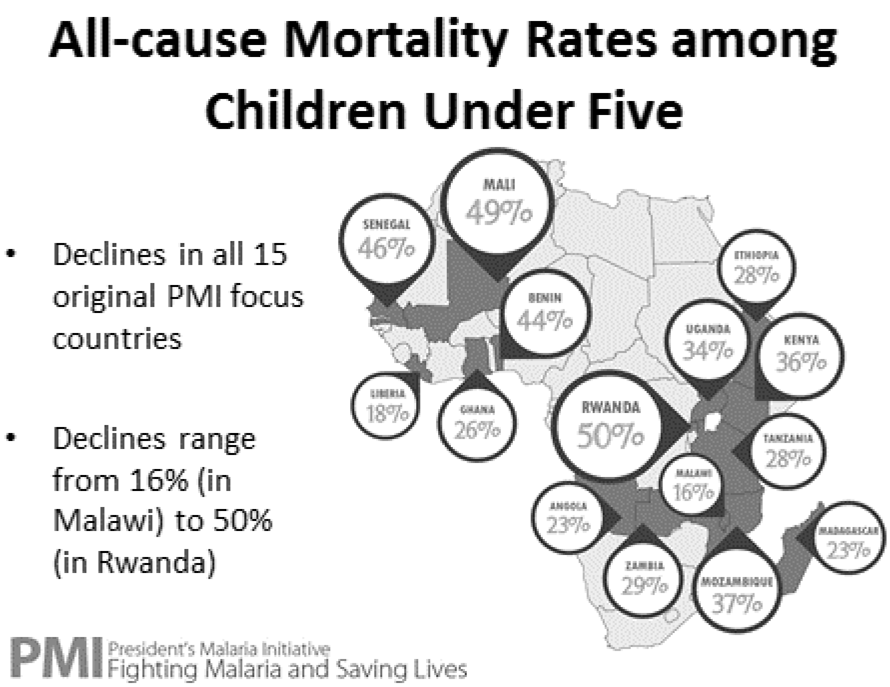


**Figure 2**




M&E: Monitoring and Evaluation
BCC: Behavior Change Coordination
HSS: Health Systems Strengthening
LLINs: Long-lasting Insecticide-Treated Nets
IRS: Indoor Residual Spraying
MIP: Malaria in Pregnancy

**Figure 3**



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