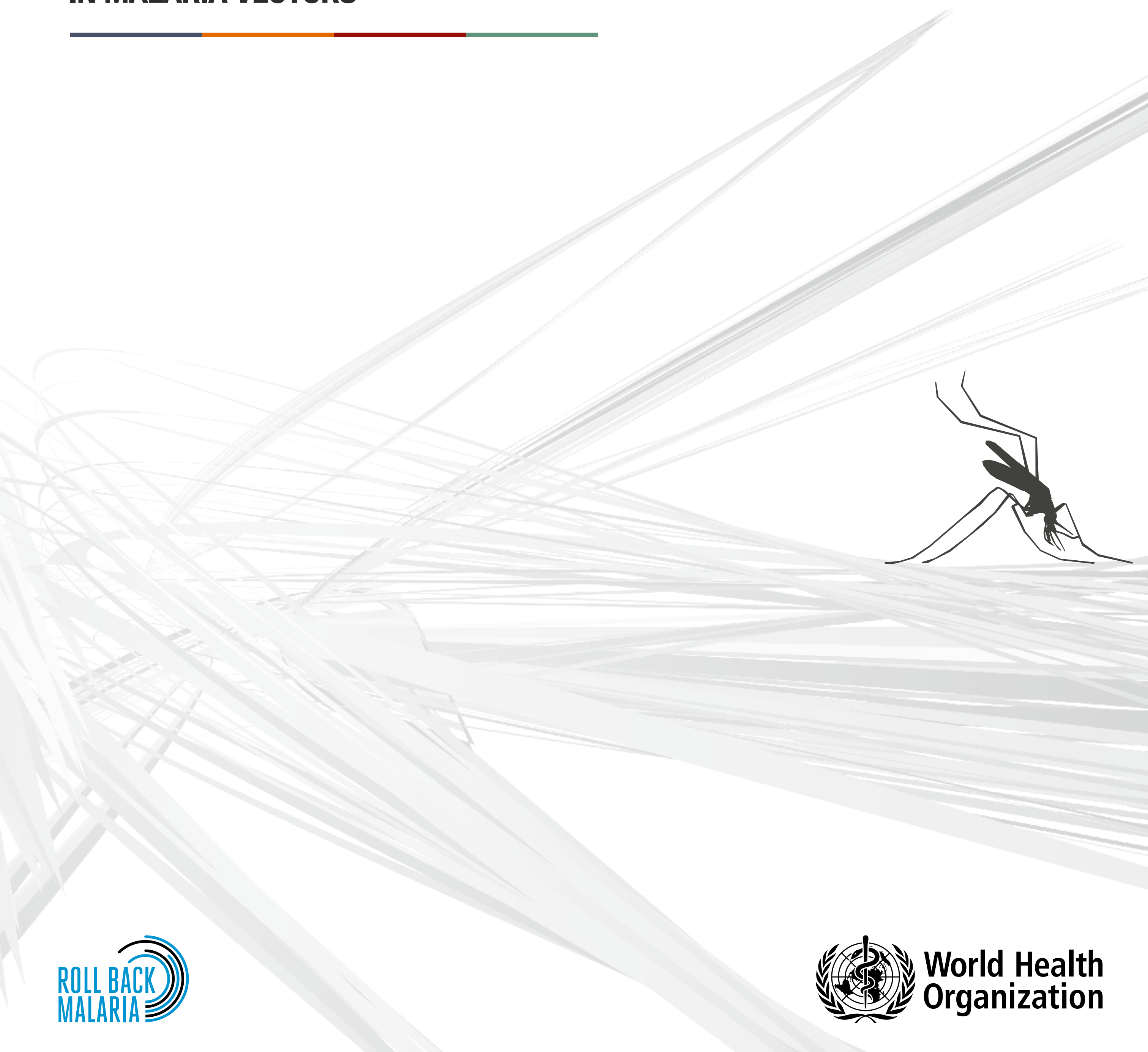
WHO GLOBAL MALARIA PROGRAMME

GLOBAL PLAN FOR INSECTICIDE RESISTANCE MANAGEMENT

IN MALARIA VECTORS

EXECUTIVE SUMMARY



ROLL BACK MALARIA

World Health Organization

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FOREWORD

The past decade has seen unprecedented progress in malaria control, resulting in major declines in malaria mortality rates globally. This progress is attributed to a significant scale-up of vector control interventions, as well as better diagnostic testing and a wider availability of effective medicines to treat malaria. But 99 countries still have ongoing malaria transmission, and the disease killed an estimated 655 000 people in 2010, mostly children under five years of age. International funding committed to malaria, while now substantial, has fallen short of the amounts needed to meet global targets. In recent years, resistance to artemisinins and other antimalarial medicines in the Mekong sub-region of Asia has become a major concern.

The next few years will be critical in the fight against malaria. Vector control, primarily through the use of indoor residual spraying and long-lasting insecticidal nets, will remain a central pillar in our efforts. The good news is that tools for controlling malaria vectors remain highly effective in almost all settings. Unfortunately, this good news is under threat: mosquitoes are developing resistance to insecticides. Insecticide resistance among *Anopheles* malaria vectors has been identified in 64 countries with ongoing malaria transmission, affecting all WHO Regions. Countries in sub-Saharan Africa and India are of greatest concern. These countries are characterized by high levels of malaria transmission and widespread reports of resistance. In some areas, resistance to all four classes of insecticides used for public health vector control has been detected.

The global malaria community takes this threat seriously. The Global Plan for Insecticide Resistance Management in malaria vectors (GPIRM) is evidence of a broad commitment to act before insecticide resistance compromises current vector control strategies. The main factor driving resistance has been the heavy reliance by vector control programmes on a single class of insecticides, the pyrethroids. In some endemic areas, the use of insecticides in agriculture also appears to have contributed to the rise of resistant mosquitoes. Urgent action is required to prevent resistance from emerging at new sites, and to maintain the effectiveness of vector control interventions in the short, medium and long term.

This GPIRM was developed in response to requests from both the World Health Assembly and the Board of the Roll Back Malaria Partnership. The WHO Global Malaria Programme gathered, analysed and synthesized input from over 130 stakeholders representing all the constituencies of the malaria control community. These include national malaria control programmes, vector control specialists, major donor organizations and multilateral and implementing agencies, as well as representatives of academic institutions, product development partnerships and industry. We trust that the GPIRM will trigger coordinated action from all stakeholders and will lay the foundations for integrated practices for managing insecticide resistance in all malaria-endemic countries.

The GPIRM puts forward a comprehensive strategy for global and country levels, including a short-term action plan with clear responsibilities, and sets out research and development priorities for academia and industry. We urge affected countries and stakeholders to take immediate action to preserve the effectiveness of current vector control methods, and to ensure that a new generation of public health insecticides is made available as soon as possible. Close collaboration between malaria control programmes and the agricultural sector will also be crucial. In addition, targeted communication and educational activities will be needed to make communities aware of the problem.

Similar to the efforts to contain emerging drug resistance, implementing the GPIRM will have cost implications in the near term, for which many malaria endemic countries will need support. We are convinced, however, that such investment now will result in significant savings in the long run, improving the sustainability and public health impact of malaria interventions, especially on maternal and child health. We have the tools at hand to end deaths from malaria. But only through concerted action will we manage to maintain the effectiveness of our existing package of interventions. If our efforts succeed, we can overcome resistance to insecticides, and save millions of lives.

Dr Margaret Chan
Director-General
World Health Organization

EXECUTIVE SUMMARY

PART 1 THE THREAT OF INSECTICIDE RESISTANCE

1.1 MALARIA VECTOR CONTROL TODAY

The control of malaria currently relies on a handful of insecticide classes and on pyrethroids in particular.

Vector control is a central, critical component of all malaria control strategies. It relies primarily on two interventions: long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS). Use of both has increased significantly during the past 10 years as part of a drive towards universal coverage of all populations at risk, saving hundreds of thousands of lives.

The active ingredients of all WHO-recommended products for IRS come from only four classes of insecticide: pyrethroids, organochlorines (dichlorodiphenyltrichloroethane, DDT), organophosphates and carbamates. All currently recommended LLINs are treated with pyrethroids. From the points of view of both safety and effectiveness, pyrethroids are the best insecticides ever developed for public health use. They accounted for the majority of IRS coverage worldwide in 2009 and were used in all LLINs (*1*). The reliance of modern malaria control on pyrethroids and the increasing resistance of malaria vectors to these products put current global efforts at risk.

For these reasons, a group of experts was convened by WHO in 2010 to identify technical strategies for preserving the effectiveness of the insecticides used for malaria control (*2*). The Global Plan for Insecticide Resistance Management in malaria vectors is a further stage in preparing a global strategy, setting out the rationale and an action plan for insecticide resistance management (IRM) by a broad-based stakeholder community.

1.2 STATUS OF INSECTICIDE RESISTANCE

Insecticide resistance is widespread: it is now reported in nearly two thirds of countries with ongoing malaria transmission. It affects all major vector species and all classes of insecticides.

The significant increase in insecticide-based malaria vector control in the past decade has resulted in increasing resistance among malaria vectors because of the selection pressure placed on resistance genes. Data are still limited and difficult to consolidate as many countries have not yet carried out adequate routine susceptibility testing. But at the time of this report's publication, resistance to at least one insecticide had been identified in 64 countries with ongoing malaria transmission. Resistance to pyrethroids seems to be the most widespread.

For the time being, existing vector control tools remain highly effective in most settings but their effectiveness can only be maintained through urgent and concerted action by the global malaria community. Countries in sub-Saharan Africa and India are of greatest concern because of the combination of widespread reports of resistance—in some areas to all classes of insecticides—and high levels of malaria transmission.

Managing insecticide resistance is complex, in part because resistance takes a variety of forms. Therefore, local strategies must be tailored to the type of resistance present. The two main mechanisms—metabolic resistance[1] and target-site resistance[2]—include multiple forms[3], which are of varying importance for different classes of insecticide. A further complication is 'cross-resistance' between insecticides that have the same mode of action for killing mosquitoes. For example, vectors that are resistant to pyrethroids and have *kdr* target-site resistance will probably also be resistant to DDT. Cross-resistance restricts the choice of alternative insecticide available for resistance management.

Most experts consider that insecticide resistance will likely have significant operational impact if no pre-emptive action is taken.

There has been one broadly accepted case of control failure due to metabolic resistance to pyrethroids used in an IRS programme in South Africa in 2000. Data from experimental hut trials also suggest that resistance could contribute to a lower-than-expected level of control. Some experts are concerned there may be other such examples that have gone undetected because of the difficulty in linking increases in malaria cases to evidence of resistance. While further evidence is clearly needed to understand more about the operational impact of insecticide resistance on the effectiveness of vector control interventions, this should not prevent the malaria community from taking action now.

The evolution of insecticide resistance is of great concern; we must act early, before resistance becomes stable in the vector populations.

Immediate action is particularly important given the evolution of resistance. Resistance genes have spread rapidly in malaria vector populations over large areas. Data also suggest that resistance can evolve swiftly, occurring at low frequency for many years without being detected and then increasing rapidly to very high levels, to a stage at which it becomes less likely or even impossible to reverse the trend. Resistance can probably be reversed only if the vector incurs a 'fitness cost' for being resistant (if the resistance gene confers some disadvantage on these vectors in comparison with susceptible populations). Once the insecticide is changed, these resistant mosquitoes will no longer have an advantage, and will die out.

Some IRM strategies (e.g. rotations) are based on this concept — that removing selection pressure will reverse resistance, and that it may therefore be possible at some point to reintroduce the original insecticide into vector control programmes. Insecticide resistance management strategies must, however, be implemented before the resistance gene becomes common and stable in the population; otherwise, the resistant gene will not recede even if use of the insecticide causing selection pressure is discontinued.[4]

Current monitoring of insecticide resistance is inadequate and inconsistent in most settings in which vector control interventions are used. Often, monitoring is performed reactively or ad hoc, depending on local research projects being conducted. In addition, the limited availability of reliable routine monitoring data from epidemiologically representative sites makes decision-making on managing insecticide resistance difficult.

1 Metabolic resistance is mediated by a change in the enzyme systems that normally detoxify foreign materials in the insect; resistance can occur when increased levels or modified activities of an enzyme system cause it to detoxify the insecticide much more rapidly than usual, thus preventing it from reaching its intended site of action.

2 Target-site resistance occurs when the molecule that the insecticide normally attacks (typically within the nervous system) is modified, such that the insecticide no longer binds effectively to it, and the resistant insect is therefore unaffected, or less affected, by the insecticide.

3 At the target site, resistance mutations can affect either acetycholinesterase or voltage-gated sodium channels. The gene for this type of resistance is known as *knock-down resistance (kdr)*. For metabolic resistance, three enzyme systems are important: esterases; mono-oxygenases and glutathione *S*-transferases.

4 As demonstrated by a study of blowflies by McKenzie and Whitten in 1982 (*3*), fitness cost is not an intrinsic property of the gene. Therefore, if that gene is allowed sufficient time to become common in a population, the rest of the genome will adapt to incorporate it without a significant fitness cost. At this point, even if the selection pressure is removed, the resistance gene will remain in the population.

1.3 POTENTIAL EFFECT OF RESISTANCE ON THE BURDEN OF MALARIA

If nothing is done and insecticide resistance eventually leads to widespread failure of pyrethroids, the public health consequences would be devastating: much of the progress achieved in reducing the burden of malaria would be lost.[1]

For example, current coverage with LLINs and IRS in the WHO African Region is estimated to avert approximately 220 000 deaths among children under 5 years of age[2] every year. If pyrethroids were to lose most of their efficacy, more than 55% of the benefits of vector control would be lost, leading to approximately 120 000 deaths not averted.[3] If universal vector control coverage were achieved, insecticide resistance at this level would be even more detrimental if pyrethroids failed, with approximately 260 000 deaths of children under 5 years of age not averted every year.

The community currently has a window of opportunity to act, to ensure that malaria vector control interventions continue to be a pivotal component of malaria control, as endemic countries attain universal coverage with sustained malaria control and elimination.

1.4 AVAILABLE STRATEGIES FOR MANAGING RESISTANCE

Strategies to preserve the efficacy of insecticides have already been used in public health and agriculture; there is no magic wand to break resistance, but several strategies of proven use could delay the spread of resistance, at least until new classes of insecticides and new tools become available.

With the potential impact on the malaria burden in mind, action can and should be taken now. IRM, with the objective of preserving or prolonging the susceptibility of malaria vectors to insecticides in order to maintain the effectiveness of vector control interventions, is not a novel concept; it was used effectively in agriculture during the past century as well as in public health (e.g. in the Onchocerciasis Control Programme in the 1980s). As continued exposure to a given insecticide eventually results in resistance to that insecticide, IRM strategies and judicious use of insecticides are required in any programme in which insecticides are used.

Several strategies exist for IRM for vector control, which are based on use of IRS and LLINs. They include: rotations of insecticides, use of interventions in combination and mosaic spraying. Potential future strategies include use of mixtures. In some settings, resistance management strategies may be implemented in the broad context of integrated vector management. These strategies can have several effects on populations of resistant vectors: they can delay the emergence of resistance by removing selection pressure (e.g. rotations) or kill resistant vectors by exposing them to multiple insecticides (e.g. mixtures, when they become available).

1 All assumptions for the estimates provided here can be found in the main document.
2 Current coverage with LLINs and IRS interventions as reported in the WHO *World Malaria Report 2010* and assuming an estimated efficacy of IRS and LLINs of ~55% on malaria-related child mortality.
3 Assuming 25% efficacy for LLINs, 10% for pyrethroid-based IRS, 55% for non-pyrethroid-based IRS; sensitivity analysis included in the main document.

PART 2 COLLECTIVE STRATEGY AGAINST INSECTICIDE RESISTANCE

2.1 OVERALL MALARIA COMMUNITY STRATEGY

The global strategy consists of five activities (described as five 'pillars') spanning the short, medium and long term. Although some will be led by countries and others at global level, implementing all five pillars is the shared responsibility of all members of the malaria community.

The long-term goal of the malaria community is to maintain the effectiveness of vector control. It is our collective obligation to act in a coordinated manner against insecticide resistance immediately, in order to ensure the continued effectiveness of current and future malaria vector control tools to prevent malaria transmission, morbidity and mortality.

In the near term, prudent action should be taken to preserve the susceptibility of major malaria vectors to pyrethroids and other classes of insecticides, while making investments to ensure that new options for large-scale vector control become available as rapidly as possible.

The five pillars of the GPIRM are illustrated in Figure 1. Some of the activities (particularly pillars I and II) must be country driven but will require strong support from international partners. Although all countries are important to the success of the global strategy to manage insecticide resistance, in a resource-constrained environment, action is especially urgent in some high-priority areas,[1] particularly in sub-Saharan Africa.

Figure 1: Five pillars of the Global Plan for Insecticide Resistance Management in malaria vectors