GLOBAL PLAN FOR ARTEMISININ RESISTANCE CONTAINMENT

ROLL BACK MALARIA

World Health Organization

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WHO Library Cataloguing-in-Publication Data

Global plan for artemisinin resistance containment (GPARC).

1.Antimalarials – therapeutic use. 2.Artemisinins – therapeutic use. 3.Drug resistance. 4.Malaria – drug therapy. 5.Plasmodium falciparum – drug effects. 5.Health programs and plans. I.World Health Organization. II.Global Partnership to Roll Back Malaria.

ISBN 978 92 4 150083 8 (NLM classification: QV 256)

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Design and layout: paprika-annecy.com
Photo credit: Image licensed by Ingram Publishing
Layout coordination and maps: Claudia Corazzola, WHO/GRA
Cover: Photo retouching and Illustration by Denis Meissner, WHO/GRA

Printed by WHO/DUP

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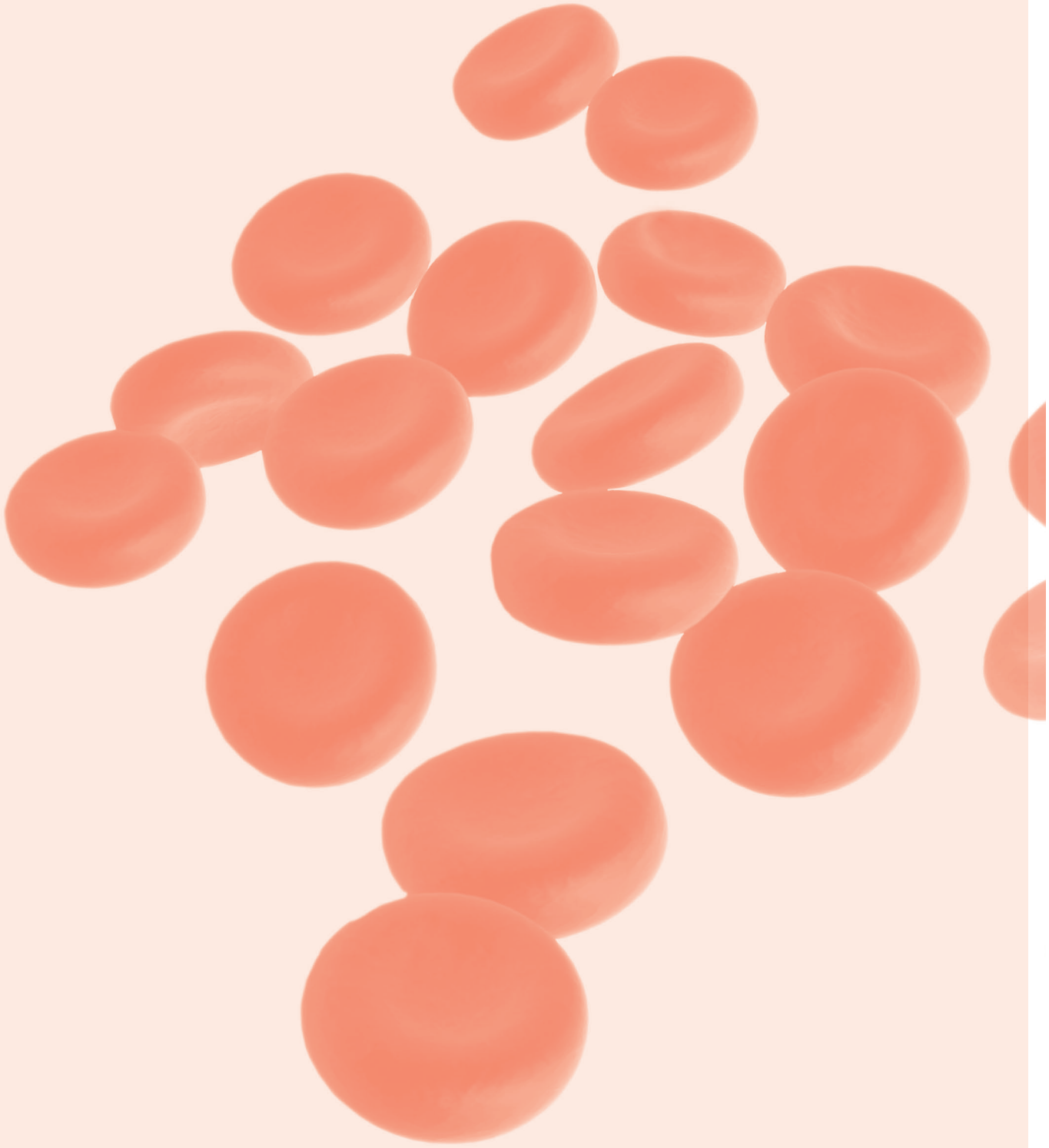

Acknowledgements

The *Global Plan for Artemisinin Resistance Containment* (GPARC) was developed in consultation with members of each of the constituencies of the Roll Back Malaria Partnership. The work was coordinated by the World Health Organization (WHO) Global Malaria Programme, with the direct support of The Boston Consulting Group and funding from the Bill & Melinda Gates Foundation. WHO Global Malaria Programme would like to thank the many individuals and institutions that participated in the preparation of the GPARC for invaluable advice provided through interviews and consultations, comments on the initial fact base on artemisinin resistance or review of the final document.

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The final draft was edited by Elisabeth Heseltine.

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Abbreviations

ACT	artemisinin-based combination therapies
ARCE	artemisinin resistance containment and elimination
GFATM	The Global Fund to Fight AIDS, Tuberculosis and Malaria
GPARC	Global Plan for Artemisinin Resistance Containment
PCR	polymerase chain reaction
RBM	Roll Back Malaria
RDT	rapid diagnostic test
USA	United States of America
WHO	World Health Organization

Foreword

Stepped up efforts to control malaria are producing impressive results. Over the past decade, the number of malaria cases has fallen by more than half in 40% of malaria endemic countries, and estimates suggest that nearly 750 000 lives have been saved in Africa alone. But this progress is fragile. One of the major threats to sustained malaria control and elimination is the emergence of malaria parasites that are resistant to artemisinins. These medicines are the basis for artemisinin-based combination therapies (ACTs), our most potent weapon in treating falciparum malaria.

Evidence of resistance to artemisinins has been identified and confirmed on the Cambodia-Thailand border. Other suspected foci have been identified in the Greater Mekong subregion, but are not yet confirmed. Although the extent of the problem is still being investigated, the world needs to mobilize immediately to contain artemisinin resistance in these hotspots and to stop its spread to new areas. The threat must be taken seriously. Resistance to previous generations of antimalarials spread rapidly around the world, resulting in increases in child mortality and an untold number of deaths. We believe containing and preventing artemisinin resistance is achievable, but it will require a commitment to both accelerate malaria control efforts and implement a modest number of additional activities.

The *Global Plan for Artemisinin Resistance Containment* (GPARC) is a call to action for all members of the Roll Back Malaria (RBM) Partnership. The document is a companion to the *Global report on antimalarial drug efficacy and drug resistance: 2000–2010*, which provides the extensive evidence on which the GPARC was based. The GPARC sets out a high-level plan of attack to protect ACTs as an effective treatment for *Plasmodium falciparum* malaria.

WHO, working with affected countries and with support from a variety of donors and partners, has taken a leading role in characterizing artemisinin resistance and in efforts to contain it in the Greater Mekong subregion. WHO will continue to be closely involved in this effort and will work to coordinate global implementation of the GPARC. Given the need for a broad-based response, successful implementation of the GPARC will require the commitment not only of the many stakeholders from the malaria community but also from non-health sectors including education, finance, and immigration.

Endemic countries are on the front line of resistance management, and they should lead implementation of the GPARC. To be successful, they will need support, both financial and technical, to translate the global plan into an operational program – customized to their regional specificities and level of threat – and to implement it at the local level. The WHO Global Malaria Programme, as well as WHO Regional and Country Offices together with RBM partners, will support endemic countries to put simple and effective plans into place to contain or prevent resistance. Endemic countries will also need support from nongovernmental organizations, private sector, academic institutions and other partners, as well as additional funding for implementation. Ultimately, we must all come together to act now if we are to sustain the gains we have made so far and reach the health-related Millennium Development Goals.

Dr Margaret Chan
Director-General
World Health Organization

Executive summary

PURPOSE OF THE PLAN

The goal of the GPARC is to protect ACTs as an effective treatment for *P. falciparum* malaria. The GPARC comes at a critical juncture. Artemisinin[1] resistance has been confirmed in a limited area within the Greater Mekong subregion, and evidence from other potential foci in this region is being reviewed. Experts agree that there is a limited window of opportunity to contain or eliminate the resistant parasites before they spread to areas of higher transmission, putting at risk recent progress in malaria control. The urgency is increased by the fact that no other antimalarial medicines are available that offer the same level of efficacy and tolerability as ACTs, and few promising alternatives are available in the immediate research and development pipeline. While efforts to contain and prevent artemisinin resistance at global and local levels have begun, they are not sufficient and must be expanded, intensified and better coordinated.

The GPARC is intended to mobilize global and local stakeholders for the containment and ultimate elimination of artemisinin resistance where it has emerged and for the prevention of its emergence in or spread to new locations. While economic development, improvements to health systems, and integrated efforts to improve maternal and child health, will also improve management of malaria and resistance, these activities are beyond the scope of this document. The objectives of the GPARC are to:

- define priorities for the containment and prevention of artemisinin resistance;
- motivate action and describe responsibilities by constituency;
- mobilize resources to fund the containment and prevention of artemisinin resistance;
- increase collaboration and coordination for artemisinin resistance containment and prevention among relevant stakeholders; and
- define governance mechanisms and indicators for continual assessment of progress made in implementing the GPARC.

The GPARC was developed by the WHO Global Malaria Programme through consultation with over 100 malaria experts. The GPARC builds on a WHO Global Malaria Programme S*trategy paper on management of antimalarial drug resistance* presented at the Seventeenth RBM Board meeting in December 2009. As many of the activities involved in containing and preventing artemisinin resistance are consistent with good malaria control, the GPARC also builds on existing WHO policies and guidelines for malaria and on the RBM *Global Malaria Action Plan*. The GPARC is not a synthesis of the literature on malaria control, but addresses the additional actions needed to prevent artemisinin resistance. It does not represent policy or technical guidance but is rather a call to action and a high-level plan of attack. For technical guidance in making an operational plan, including country-specific operational goals and timelines, national malaria control programmes should refer to the WHO guidelines for malaria control and elimination available on the WHO Global Malaria Programme website and can consult their regional offices for assistance and support (http://www.who.int/malaria).

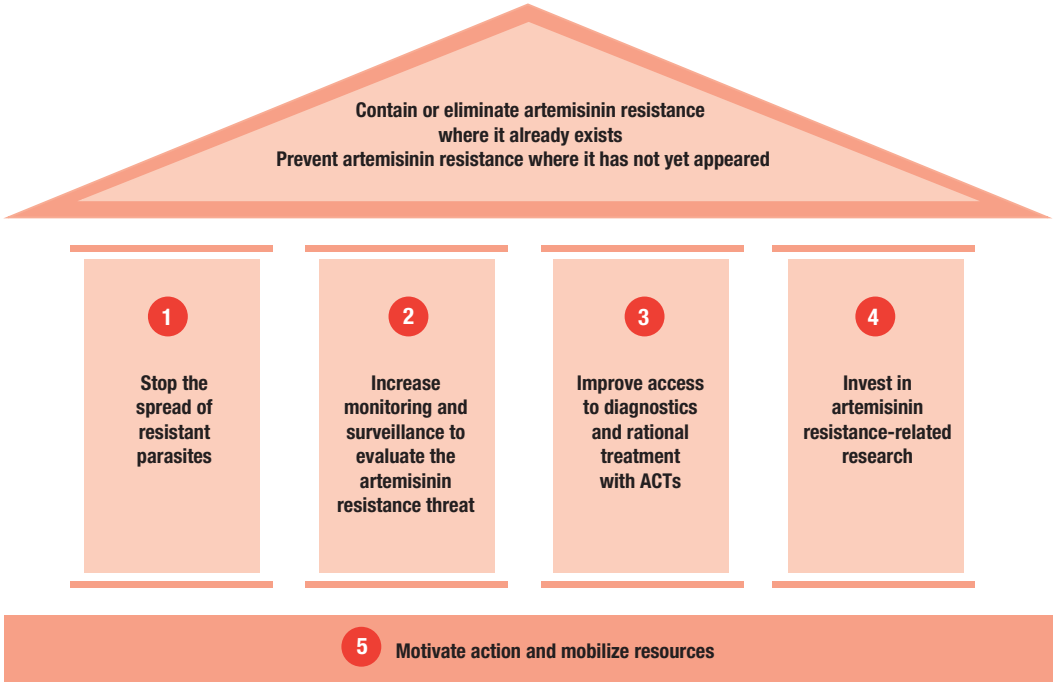
[1] Unless otherwise indicated, the word 'artemisinin' is used in this document to refer to artemisinin and its derivatives, artesunate, artemether and dihydroartemisinin.

ISSUES AND RECOMMENDATIONS

While many unknowns remain with regard to artemisinin resistance, several commonly accepted hypotheses form the basis of the response outlined in the GPARC. In particular, experts agree that common failures in malaria control programmes are likely to contribute to the emergence and spread of artemisinin resistance. Challenges in each component of malaria control – routine monitoring, prevention, diagnosis and treatment – must be addressed. Thus, one of the most important components of successful artemisinin resistance containment and prevention is intensified, sustained malaria control or elimination in all endemic regions.

Given the emergence of artemisinin resistance in the Greater Mekong subregion and the threat of its spread to other areas, additional resistance containment activities are required to prevent the loss of ACTs as effective treatment. The activities described in Figure 1 are all important for successful management of artemisinin resistance. Applying these recommendations immediately in areas for which there is credible evidence of resistance is of the utmost priority.

FIGURE 1. GPARC goals and recommendations



1. **Stop the spread of resistant parasites.** In areas for which there is evidence of artemisinin resistance, an immediate, comprehensive response with a combination of malaria control and elimination measures is needed to stop the survival and spread of resistant parasites. In areas without known resistance, malaria control can reduce transmission, lowering the risk that resistant parasites will spread into those regions and minimizing the potential public health effect if resistance were to take hold. Increased coverage with preventive measures, especially vector control, is a priority, as are programmes to control malaria in mobile and migrant populations. Where artemisinin resistance is confirmed, national malaria control programmes may also consider a range of epidemiological or transmission-reduction tools, including focused screening and treatment, active case detection, mass screening and treatment or mass drug administration, in accordance with the latest evidence and guidelines.

2. **Increase monitoring and surveillance to evaluate the threat of artemisinin resistance.** Regular monitoring and surveillance are critical to identify new foci rapidly and to provide information for containment and prevention activities. WHO recommends that countries endemic for malaria perform routine monitoring of antimalarial drugs at sentinel sites every 24 months in order to detect changes in their therapeutic efficacy (WHO, 2009). An immediate priority is to assess ACT therapeutic efficacy in countries where no studies have been performed in the previous 2 years. Emphasis should be placed on data quality. Regions for which there is evidence of resistance should consider adding further sentinel sites to facilitate early detection of additional foci. In high-risk areas, especially in those with no active sentinel sites, routine surveillance of confirmed malaria cases, deaths and (especially) treatment failures should be strengthened.

3. **Improve access to diagnostics and rational treatment with ACTs.** Increasing access to affordable, quality-assured diagnostics and treatment with ACTs improves patient outcomes and limits opportunities for resistance to both artemisinins and partner drugs (WHO, 2010a). Programmes should include complementary activities to ensure consistent, accurate diagnostic testing, better access to ACTs for confirmed cases, compliance with ACT treatment and removal of oral artemisinin-based monotherapies and substandard and counterfeit drugs. Education and communication campaigns focused on diagnosis and treatment, with messages tailored to patients, providers and retailers, should be a component of these efforts.

4. **Invest in artemisinin resistance-related research.** Research is important to improve understanding of resistance and the ability to manage it. Research in five disciplines should be a priority: laboratory research (e.g. to identify a molecular marker for artemisinin resistance), research and development (e.g. of novel non-artemisinin-based antimalarial combinations), applied and field research (e.g. pilot studies of transmission reduction tools, such as mass screening and treatment or mass drug administration), operational research (e.g. scalable[2] programmes for mobile populations) and mathematical modelling (e.g. of the potential impact of resistance on the malaria burden).

5. **Motivate action and mobilize resources.** Successful implementation of the GPARC will depend on motivating many stakeholders at global, regional and national levels to support or conduct the recommended activities. Additional funding will be required, and leadership and sustained cooperation in the malaria community will be needed to stimulate relevant individuals, organizations and governments to support artemisinin resistance containment and prevention.

[2] In the context of this document, 'scalable' refers to expanding the scope of a tool or programme to reach a larger population or area.

APPLYING RECOMMENDATIONS AT COUNTRY LEVEL

In view of regional differences and varying levels of artemisinin resistance, each endemic country is expected to evaluate its level of risk and then to apply the GPARC recommendations accordingly in designing a containment or prevention programme. Different levels of response may be required for different areas in a country.

In areas for which there is credible evidence of artemisinin resistance, defined as 'tier I', an immediate, multifaceted response is recommended to contain or eliminate resistant parasites as quickly as possible. As described in the *Global report on antimalarial drug efficacy and drug resistance, 2000–2010* (section 4.5, Figures 24 and 25), tier I areas included several suspected foci in the Greater Mekong subregion in November 2010. As the situation is evolving, readers should consult the WHO Global Malaria Programme website (http://www.who.int/malaria) for the most recent evidence. In tier I areas, malaria control efforts should be accelerated to reach universal coverage of at-risk populations as soon as possible, with the aim of universal parasitological diagnostic testing, access to and rational use of quality-assured ACTs for all confirmed malaria cases, use of primaquine as appropriate to block transmission and use of suitable vector control. Specific activities to contain or eliminate resistant parasites should also be implemented, including increased monitoring of ACT therapeutic efficacy around known foci, programmes for mobile and migrant populations, enforcement to eliminate the use of oral artemisinin-based monotherapies and poor-quality drugs, and consideration of epidemiological or transmission-reduction tools. Regular monitoring, evaluation and timely reporting of progress to a central, publicly available site is another important component of tier I containment programmes.

Tier II areas are those with significant inflows of mobile and migrant populations from tier I areas or shared borders with tier I areas. The recommendations for tier II countries are intensified malaria control to reduce transmission and limit the risk for emergence or spread of resistant parasites, with access to parasitological diagnostic testing, quality-assured ACTs for confirmed malaria cases (plus primaquine as appropriate), elimination of oral artemisinin-based monotherapies and poor-quality drugs and effective coverage with suitable vector control. Countries with tier II areas should also implement activities to manage the spread of resistance, including programmes to reach mobile and migrant populations. Activities to increase monitoring of the therapeutic efficacy of ACTs in high-risk areas should be considered in order to detect and report possible new foci rapidly.

In tier III areas, defined as *P. falciparum* endemic areas which have no evidence of artemisinin resistance and limited contact with tier I areas, prevention and preparedness should focus on scaling up control measures to increase coverage with parasitological diagnostic testing, quality-assured ACTs and vector control. Tier III areas should also routinely monitor the therapeutic efficacy of ACTs in order to detect signs of emerging resistance promptly. In countries where oral artemisinin-based monotherapies or poor-quality drugs are used extensively, regulation and enforcement should be increased to eliminate the use of these products.

ROLE OF STAKEHOLDERS

Most malaria control and elimination activities are also of benefit for the containment and prevention of artemisinin resistance. Stakeholders are encouraged to continue and, where possible, expand or accelerate the malaria control activities that they conduct or support. The GPARC will help stakeholders to identify and understand additional areas to which they can contribute in order to manage artemisinin resistance.

The GPARC was designed with input from all of the constituencies of the RBM Partnership and is intended to motivate actions among each of these groups. Given the complexity of the required response to artemisinin resistance, stakeholders outside the traditional malaria or public health communities will also have to be engaged. The priorities for action by constituency are shown in Table 1 and are described in more detail in chapter 9 of the GPARC.

TABLE 1. Primary and secondary areas of involvement by stakeholder segment

	Global policy and norms	Surveillance and reporting	Containment and implementation	Resource mobilization	Advocacy and political engagement	Research	Local policy and regulation	Emergency response
Endemic countries (tier I, II and III)	✓	✓	✓	✓	✓	✓	✓	✓
Multilateral organizations WHO Global Malaria Programme	✓	✓	✓	✓	✓	✓*	✓	✓
Multilateral organizations WHO regional and country offices	✓	✓	✓	✓	✓		✓	✓
Multilateral organizations all other			✓	✓	✓			✓
Research and academia		✓		✓	✓	✓		
Nongovernmental organizations			✓	✓	✓			✓
Private sector		✓	✓	✓	✓	✓		✓
Funding agencies and bilateral donors		✓	✓	✓	✓	✓	✓	✓

✓ Primary ✓ Secondary

* Research part conducted by Special Programme for Research and Training in Tropical Diseases, WHO.

The GPARC will be implemented mainly by malaria-endemic countries, which will have a major role in all functions. Given WHO's mandate to represent and support countries, the areas of involvement of WHO Global Malaria Programme will mirror those of countries, focusing on policy guidance, global surveillance and technical expertise. Having led the development of the GPARC, WHO Global Malaria Programme will continue to oversee and coordinate its implementation. In order to do so, a new unit dedicated to antimalarial drug resistance has been created, the Drug Resistance and Containment unit. WHO Global Malaria Programme will rely on WHO regional and country offices to coordinate assessments of the threat of artemisinin resistance, prepare detailed and actionable response plans, build capacity for monitoring and mobilize the necessary stakeholders and resources.

Successful implementation of the GPARC will depend on the support and cooperation of many other groups. For example, research and academic institutions may lead the planning and execution of artemisinin resistance-related research and support surveillance and reporting; they may play a secondary role in resource mobilization and advocacy. Funding agencies, including The Global Fund to Fight AIDS, Tuberculosis and

Malaria (GFATM) and bilateral donors, have a primary role in resource mobilization, advocacy and political engagement. As funders, their support is critical to the success of all activities. Nongovernmental organizations will play a primary role as partners of national malaria control programmes in implementing containment and prevention programmes and will support resource mobilization and advocacy. The private sector has a variety of cross-cutting roles to play, including support of containment programmes, advocacy and research.

RESOURCE MOBILIZATION

Given the overlap between malaria control and artemisinin resistance containment, a fully funded and implemented malaria control agenda, as outlined in the *Global Malaria Action Plan,* would address many of the needs for the containment and prevention of artemisinin resistance. Nonetheless, additional funding will be needed for specific initiatives to manage artemisinin resistance, the immediate priority being funding for programmes in current tier I and II areas.

On the basis of experience with the programme for artemisinin resistance containment and elimination (ARCE) in Cambodia and Thailand, tier I and II containment and prevention programmes are estimated to cost US$ 10–20 and US$ 8–10 per person at risk annually, respectively. The exact cost will depend on the intensity of the effort required and the existing capacity and infrastructure. Additional funding will be needed for tier III programmes and also for global and regional coordination of GPARC implementation. The estimated cost for accelerating research and development of non-artemisinin-based antimalarial medicines and high-priority laboratory research is US$ 60–65 million annually. In total, full funding of artemisinin resistance containment and prevention would be upwards of US$ 175 million per year globally, with just over US$ 100 million for programme support. These estimates are based on the assumption that tier I and II areas are limited to those in and around the currently suspected foci in Cambodia, Myanmar, Thailand and Viet Nam.

A relatively small investment in containment now, before artemisinin resistance spreads beyond the Greater Mekong subregion, will avoid a much larger subsequent investment. If artemisinin resistance emerges in another region, the costs of managing it will increase dramatically, particularly if the affected region has high malaria transmission. Despite recent increases in malaria funding, however, there is still a significant shortfall for both malaria control and artemisinin resistance containment and prevention. This funding gap presents a risk for both malaria control and artemisinin resistance activities. In order to contain resistance successfully, the funding gap must be reduced, requiring greater global and country engagement and more focus and cooperation among stakeholders.

MEASUREMENT AND EVALUATION

Measurement, evaluation and transparent reporting of the GPARC's implementation are critical to the successful management of artemisinin resistance. Not only do regular reporting and tracking of key indicators motivate action, but the availability of timely, good-quality data is essential to evaluate the evolving threat of artemisinin resistance, track progress in managing it and guide future containment and prevention activities.

Measurement and evaluation should be conducted at all levels – global, regional, national and area (tier) – and should include regular, formal reporting. Evaluation will cover a mix of process, outcome and impact measures. To minimize resources, the measures will, where possible, be based on data that are already collected for malaria control and elimination. Continued cooperation with the research community will further widen and deepen the pool of available information. In some cases, new indicators, and processes to measure them, will be identified and developed. Data quality should be a strong focus, as a useful

assessment of the progress of the GPARC will rely on good data. WHO Global Malaria Programme will lead global coordination in tracking and communication of key indicators. In order to ensure independent, transparent evaluation of progress and achievements, WHO Global Malaria Programme will establish a technical expert group on drug resistance to review and evaluate progress reports regularly.

EMERGENCY MOBILIZATION

The GPARC was designed on the basis of current knowledge about where artemisinin resistance exists and on assumptions about the timeframe for its potential spread. The seriousness of the situation today requires an immediate, intense, well-coordinated response. Should artemisinin resistance spread more rapidly than originally anticipated, an escalated response will be required. The emergency mobilization plan outlined in the GPARC has three elements: global advocacy to place artemisinin resistance at the top of health and development agendas; intensive, coordinated containment activities in areas with newly confirmed artemisinin resistance; and a significant increase in funding. The emergency mobilization plan builds on the recommendations outlined in the GPARC but adds intensity and magnitude to meet the increased threat.

ISSUES AND RECOMMENDATIONS

There is a finite window of opportunity to contain artemisinin resistance before it spreads. If the current foci of artemisinin-resistant parasites are not contained or eliminated, the costs, both human and financial, could be great. Areas with high transmission and low coverage with malaria interventions are particularly vulnerable to increases in malaria-related morbidity and mortality. If artemisinin resistance were to take hold in such regions, continued high transmission could lead to the rapid spread of resistant parasites and the eventual loss of ACTs as an effective treatment, potentially resulting in a significant increase in malaria-related deaths. Thus, while the first priority is immediate implementation of containment programmes in the Greater Mekong subregion, it is also important to focus on prevention and preparedness, including sustainable surveillance, in other malaria-endemic countries. The global community must come together now to address this significant threat before the situation deteriorates.

Introduction

PURPOSE OF THE PLAN

The goal of the GPARC is to protect ACTs for treatment of *P. falciparum* malaria. The GPARC comes at a critical juncture. Artemisinin resistance has been confirmed in a limited area within the Greater Mekong subregion, and evidence from other potential foci in this region is under review. Experts agree that we have a limited window of opportunity to contain or eliminate the resistant parasites before they spread to higher-transmission areas, putting at risk recent progress in malaria control. The urgency is increased by the fact that no other antimalarial medicines are available that offer the same levels of efficacy and tolerability as ACTs, and few promising alternatives are available in the immediate research and development pipeline. While efforts have begun at both global and local levels to prevent and contain artemisinin resistance, they are not sufficient and must be expanded, intensified and better coordinated.

The objective of the GPARC is to mobilize global and local stakeholders to contain and ultimately eliminate artemisinin resistance where it has emerged and to prevent its emergence in or spread to new locations. The GPARC is part of a larger initiative by WHO and global health partners to prevent and contain antimicrobial resistance. While economic development, improvements to health systems, and integrated efforts to improve maternal and child health, will also improve management of malaria and resistance, these activities are beyond the scope of this document. The objectives of the GPARC are to:

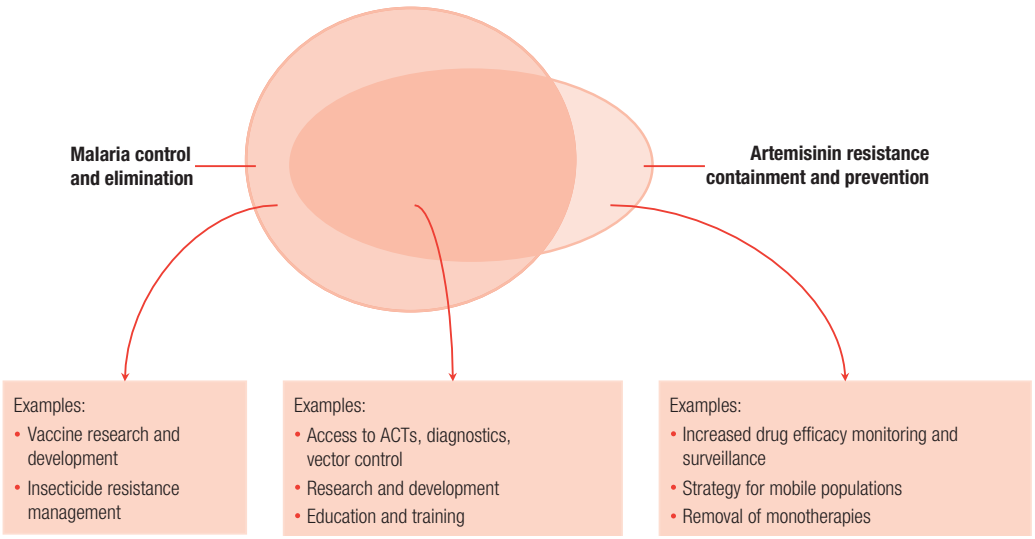
- define priorities for the containment and prevention of artemisinin resistance;
- motivate action and describe responsibilities by constituency;
- mobilize resources to fund the containment and prevention of artemisinin resistance;
- increase collaboration and coordination for artemisinin resistance containment and prevention in the malaria community and among relevant stakeholders more broadly; and
- define governance mechanisms and indicators for continual assessment of progress made in implementing the GPARC.

If the current known foci of artemisinin-resistant parasites are not contained or eliminated, the costs, both human and financial, could be great. Areas with high transmission and low coverage with malaria interventions are particularly vulnerable to increased malaria-associated morbidity and mortality. If artemisinin resistance were to take hold in such regions, continued high transmission could lead to rapid spread of resistant parasites and the eventual loss of ACTs as an effective treatment, potentially resulting in a significant increase in malaria-related deaths. Thus, while the first priority is immediate implementation of containment programmes in the Greater Mekong subregion, it is also important to focus on prevention and preparedness, including sustainable surveillance, in other malaria-endemic countries.

The GPARC was developed by the WHO Global Malaria Programme through consultation with over 100 global malaria experts. The GPARC builds on the WHO Global Malaria Programme *Strategy paper on management of antimalarial drug resistance* presented at the Seventeenth RBM Board meeting in December 2009. Because many of the activities for containing and preventing artemisinin resistance are consistent with good malaria control (Figure 2), the GPARC also builds on the RBM *Global Malaria Action Plan* and existing WHO policies and guidelines for malaria. The GPARC is not a synthesis of the existing literature on malaria control, but rather focuses on the additional actions needed to address artemisinin resistance; it does not represent policy or technical guidance but is a call to action and a high-level plan of attack. For technical guidance in preparing an operational plan, including country-specific operational goals

and timelines, national malaria control programmes should refer to existing WHO guidelines on malaria control and elimination on the WHO Global Malaria Programme website and may also consult their regional offices for assistance and support (http://www.who.int/malaria).

FIGURE 2. Overlap between malaria control and artemisinin resistance containment and prevention



Note: Not drawn to scale.

WORKING DEFINITIONS AND ASSUMPTIONS

WHO defines resistance as "the ability of a parasite strain to survive and/or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended but within tolerance of the subject" (WHO, 1967).[3] For the purposes of the GPARC, we consider that a significant increase in parasite clearance time is an early warning sign of artemisinin resistance and deserving of a response similar to that for confirmed resistance. In this document, the term 'artemisinin resistance' is a working definition used to refer to:

- an increase in parasite clearance time, as evidenced by ≥ 10% of cases with parasites detectable on day 3 after treatment with an ACT (suspected resistance); or
- treatment failure after treatment with an oral artemisinin-based monotherapy with adequate antimalarial blood concentration, as evidenced by the persistence of parasites for 7 days, or the presence of parasites at day 3 and recrudescence within 28/42 days (confirmed resistance).[4]

[3] This definition was later modified to include the sentence: "The form of the drug active against the parasite must be able to gain access to the parasite or the infected erythrocyte for the duration of the time necessary for its normal action."

[4] This definition is prone to confounding factors (known and unknown) such as splenectomy, haemoglobin abnormalities and reduced immunity.

The GPARC primarily addresses artemisinin and its derivatives, which are the common components in all ACTs. In order for ACTs as a class to remain viable, however, both artemisinins and partner drugs must be protected from parasite resistance. If resistance to one drug evolves, the other potentially acts as a monotherapy, increasing the likelihood that resistance will also be selected for the second drug. As a result, factors that select for parasite resistance to partner drugs may have consequences for artemisinins, jeopardizing ACTs as a class.

Given the many unknowns surrounding artemisinin resistance, the GPARC relies on several high-level assumptions, which establish a common starting point and serve as the basis for the recommendations (Box 1).

BOX 1. HIGH-LEVEL ASSUMPTIONS USED IN DESIGNING THE GPARC

- Exposure of malaria parasites to suboptimal doses of artemisinin is a primary cause of the spread of resistance.
- Delayed parasite clearance likely indicates reduced susceptibility, which may eventually lead to higher resistance.
- To our knowledge, artemisinin resistance exists only in the Greater Mekong subregion; however, the possibility that artemisinin resistance will arise in other areas or regions or spread beyond the Greater Mekong subregion must be considered.
- Preventing resistance to partner drugs is important. If the partner drug is not effective, the ACT becomes an artemisinin-based monotherapy, so that the parasite receives an inadequate dose of artemisinin as monotherapy.
- With sufficient resources and coordination, a molecular marker for artemisinin resistance could be found; once a molecular marker is available, it can be translated into useful surveillance tools.
- Eliminating *P. falciparum* malaria in affected regions might be necessary in order to eliminate the threat of resistance.

STRUCTURE OF THE PLAN

The GPARC and WHO's *Global report on antimalarial drug efficacy and drug resistance, 2000–2010* are companion documents. The latter provides a detailed history of artemisinin resistance and the state of the problem today, and the GPARC describes the recommended response.

The GPARC consists of 10 chapters. Chapter 1 provides the context of the plan and a brief overview of the artemisinin resistance problem. Chapter 2 summarizes the five core recommendations. Chapter 3 describes how these recommendations should be applied locally, with specific recommendations depending on the magnitude of the artemisinin resistance risk in a country or area. The next five chapters describe each of the recommendations in more detail, including the underlying issues and potential solutions. The financial requirements to support the GPARC are described in chapter 8. Chapter 9 summarizes the priorities for action by constituency; it is intended to help stakeholders identify areas in which they can contribute to implementation of the GPARC. Chapter 10 outlines an escalated response plan, with the activities that would be needed if artemisinin resistance spreads more rapidly than originally anticipated.

1. Context

HISTORY AND EVIDENCE

The global community has recently had many successes in malaria control. The number of malaria cases has fallen by more than 50% in 43 countries over the past decade (WHO, 2010b). A recent modelling analysis of malaria prevention in 34 African countries suggested that about 730 000 lives were saved between 2000 and 2010, with nearly three quarters of those since 2006 (Eisele et al., 2010). Funding commitments for malaria have increased nearly 15-fold, from approximately US$ 100 million in 2003 to nearly US$ 1.6 billion in 2010; and interest and commitment at global and country level are very high (Johansson, Cibulskis & Steketee, 2010). The current upward trajectory in funding must be maintained in order to sustain and expand these successes.

A looming threat to malaria control is the emergence of parasites that are resistant to antimalarial medicines. Resistance has developed to every antimalarial medicine used so far (see *Global report on antimalarial drug efficacy and drug resistance, 2000–2010*, section 1.2 for details), and the malaria burden rebounded due to consequent treatment failures. For example, the spread of *P. falciparum* resistance to chloroquine in the 1970s and 1980s was linked to a subsequent increase in child mortality in Africa (Trape, 2001; Dondorp et al., 2010).

As history predicted, resistance to artemisinins, the key component of all ACTs, was identified and confirmed on the Cambodia–Thailand border in a series of studies conducted between 2001 and 2009. More recently, evidence of artemisinin resistance has been reported in other areas of the Greater Mekong subregion (see *Global report on antimalarial drug efficacy and drug resistance, 2000–2010*, sections 4.1 and 4.5 for a more comprehensive discussion of the evidence from therapeutic efficacy studies, including the latest available data for the Cambodia–Thailand border). It is noteworthy that resistance to chloroquine, sulfadoxine–pyrimethamine and mefloquine all first emerged in this area. Resistance to chloroquine and sulfadoxine–pyrimethamine then spread from the Greater Mekong subregion to Africa and also emerged in and spread through other regions. We cannot be certain that the pattern of spread of artemisinin resistance will be similar to that of other antimalarial medicines. Ideally, artemisinin resistance will be contained at current foci before it causes significant treatment failures or spreads to other areas.

UNKNOWNS IN ARTEMISININ RESISTANCE

Much remains to be elucidated about the emergence and spread of artemisinin resistance. Scientists do not know the mechanism of resistance nor what definitively contributes to the emergence and spread of resistant parasites. The extent of artemisinin resistance today – and specifically whether it has spread beyond the Greater Mekong subregion – is unknown, and scientists are unable to predict whether it will emerge in new foci or how quickly it could spread from current foci. There are also unanswered questions about which tools and methods will be most effective in addressing artemisinin resistance (see *Global report on antimalarial drug efficacy and drug resistance, 2000–2010*, chapter 2 for details). Much of the information contained in the GPARC is based on knowledge and experience gained with resistance to other antimalarial medicines.

HYPOTHESES FOR THE EMERGENCE AND SPREAD OF ARTEMISININ RESISTANCE

Several commonly accepted hypotheses form the basis of the response outlined in the GPARC. In particular, experts agree that common failures in malaria control programmes contribute to the emergence and spread of artemisinin resistance. Challenges in each component of malaria control – routine monitoring, prevention, diagnosis and treatment – are described below and shown in Figure 3.

Monitoring and surveillance

WHO recommends routine monitoring of therapeutic efficacy to track antimalarial drug efficacy and guide treatment policy (WHO, 2009). As oral artemisinin-based monotherapy is not recommended for first-line treatment of uncomplicated malaria, routine monitoring is usually of the efficacy of ACTs. When therapeutic efficacy studies provide evidence of early resistance (e.g. increased proportion of patients with prolonged parasite clearance time), confirmatory studies must be conducted to determine the extent of resistance and guide action. Unfortunately, a significant number of countries endemic for *P. falciparum* do not routinely monitor ACT therapeutic efficacy, and comprehensive understanding of where artemisinin resistance exists today is not available. Without this knowledge, it is difficult to initiate appropriate containment activities, which may allow resistant parasites to survive and spread silently.

Prevention

Malaria control programmes should promote the use of preventive measures to reduce malaria transmission. Common measures include use of long-lasting insecticidal nets or other insecticide-treated products and indoor residual spraying (WHO, 2002; WHO, 2006). National malaria control programmes should also provide malaria prevention and treatment measures to mobile and migrant populations, which are believed to contribute to the spread of antimalarial resistance. Unfortunately, use of vector control tools remains inconsistent in many areas, and efforts to reach migrant and mobile populations are limited. In the absence of concerted efforts to reduce transmission, malaria continues to be transmitted, creating opportunities for resistance to spread.

Diagnosis

Parasitological diagnosis, typically with a rapid diagnostic test (RDT) or microscopy is recommended by WHO for all persons with suspected malaria to ensure that only confirmed cases receive treatment with an ACT (WHO, 2010a). In many settings, however, diagnostic tests are not used regularly, and, even when a test is used, the results are sometimes ignored. As a result, symptomatic patients are frequently treated presumptively with antimalarial medicines. The resulting overuse of ACTs may increase resistance, particularly to the longer-acting partner drugs that are a critical component of ACTs.

Treatment

WHO recommends treatment of confirmed malaria cases with a full course of quality-assured ACTs (WHO, 2010a). Lack of access to affordable, quality-assured ACTs may, however, result in use of less effective medicines, including oral artemisinin-based monotherapies, substandard and counterfeit treatments and drugs other than artemisinins, such as chloroquine or sulfadoxine–pyrimethamine. Although oral artemisinin-based monotherapies can be effective when taken for the full 7-day course, patients often stop taking them prematurely, as symptoms generally subside after only a few days. Consequently, parasites may be exposed to subcurative dosing regimens. Substandard and counterfeit drugs, which are widespread in

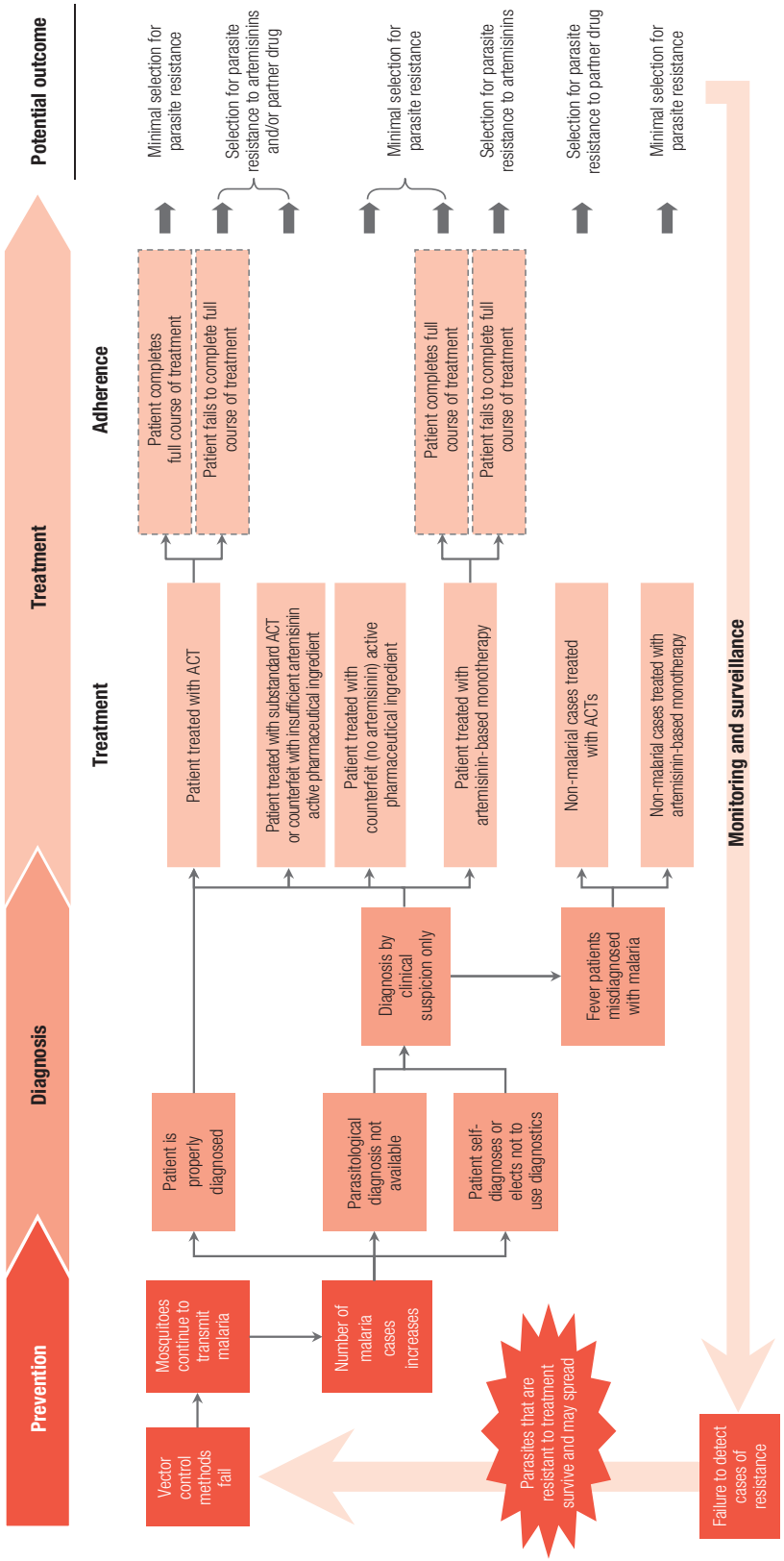


FIGURE 3. Programme failures that potentially contribute to resistance to antimalarial medicines

many endemic countries, pose a similar problem because they may contain subtherapeutic amounts of artemisinins. While sensitive parasites are eliminated, resistant parasites can multiply unrestrained and later be transmitted. These factors probably result in continuous selection in favour of the parasites that are the most resistant to either artemisinins or the partner drug.

Prevention and containment activities to date

Several efforts to contain and prevent artemisinin resistance have been initiated. For example, a multifaceted, multisectoral containment project has been launched at the Cambodia–Thailand border. These activities, coordinated by WHO and funded largely by the Bill & Melinda Gates Foundation, the GFATM and the United States Agency for International Development, are described in detail in the *Global report on antimalarial drug efficacy and drug resistance, 2000–2010* (section 4.6). Additional containment projects in other suspected foci in the Greater Mekong subregion are being discussed.

WHO, the World Health Assembly and the RBM Partnership have each called for action to address artemisinin resistance (Box 2), mainly by encouraging endemic countries to halt the marketing and use of oral artemisinin-based monotherapies. Several other organizations and programmes are also contributing to the management of resistance. For example, the WorldWide Antimalarial Research Network is a collaboration formed to facilitate research and information exchange related to antimalarial resistance. The Medicines for Malaria Venture conducts research and develops new treatments for malaria, including alternatives to artemisinin-based medicines. The MALACTRES consortium and the Broad Institute are leading activities to identify molecular markers. The United States Pharmacopeia Promoting the Quality of Medicines programme addresses substandard and counterfeit drugs in the developing world. The GFATM has launched the Affordable Medicines Facility – malaria, an innovative financing mechanism to expand access to quality-assured ACTs, which is still in the pilot phase. This list is not exhaustive, and many other organizations contribute directly or indirectly to combating antimalarial drug resistance, often by providing overall support to malaria control and elimination initiatives. These efforts could have a greater impact if there were a coordinated, global effort to increase the visibility of the issue and mobilize the malaria community and other relevant stakeholders to action. The GPARC will serve as a platform for this coordinated global effort.

BOX 2. CALLS TO ACTION ON RESISTANCE TO ARTEMISININS

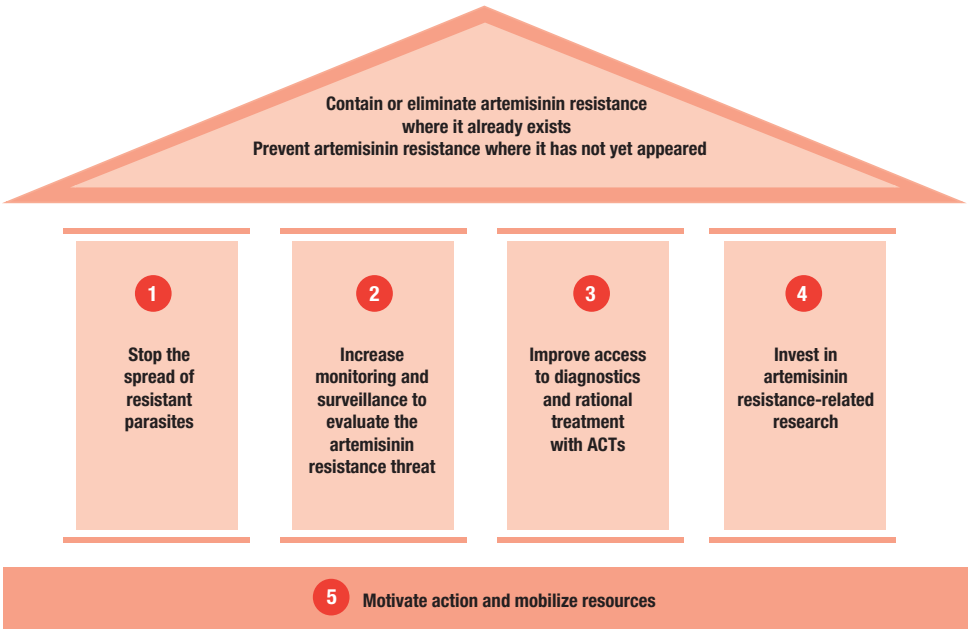
- 2005, WHO report on *Susceptibility of* Plasmodium falciparum *to antimalarial drugs*: WHO began to call attention to the danger of artemisinin resistance.
- May 2007, Sixtieth World Health Assembly: The Health Assembly adopts resolution WHA 60.18, which called for cessation of provision in both the public and the private sector of oral artemisinin monotherapies.
- September 2009, Regional Committee for Africa: The Committee adopts a resolution to encourage prevention and control of drug resistance to human immunodeficiency virus, tuberculosis and malaria treatment.
- December 2009, Seventeenth RBM Board meeting: Global Malaria Programme submits a *Strategy paper on management of antimalarial drug resistance* as requested by the Board.
- May 2010, Eighteenth RBM Board meeting: Calls for withdrawal of oral artemisinin-based monotherapies in order to prolong the usefulness of therapeutic artemisinin derivatives. A commitment to eliminate oral artemisinin-based monotherapies is signed by representatives from 40 countries.
- May 2010, World Health Assembly: The United Nations Secretary-General's Special Envoy for Malaria gives an address, emphasizing that the development and spread of artemisinin resistance could be a public health disaster.

2. Recommendations

Given the emergence of artemisinin resistance in the Greater Mekong subregion and the threat of its spread to other areas, actions to contain artemisinin resistance are required to prevent the loss of ACTs as an effective treatment. The recommendations below should be implemented both globally and locally in *P. falciparum*-endemic countries. Applying these recommendations immediately in areas for which there is credible evidence of resistance is of utmost priority.

As part of a coordinated effort to contain or eliminate artemisinin resistance where it already exists and to prevent artemisinin resistance where it has not yet appeared, the following actions should be taken (Figure 4).

FIGURE 4. GPARC goals and recommendations



1. **Stop the spread of resistant parasites.** In areas for which there is evidence of artemisinin resistance, an immediate, comprehensive response with a combination of malaria control and elimination measures is needed to stop the survival and spread of resistant parasites. In areas without known resistance, malaria control can reduce transmission, lowering the risk that resistant parasites will spread into those regions and minimizing the potential public health effect if resistance were to take hold. Increased coverage with preventive measures, especially vector control, is a priority, as are programmes to control malaria in mobile and migrant populations. Where artemisinin resistance is confirmed, national malaria control programmes may also consider a range of epidemiological or transmission-reduction tools, including focused screening and treatment, active case detection, mass screening and treatment or mass drug administration, in accordance with the latest evidence and guidelines.

2. **Increase monitoring and surveillance to evaluate the threat of artemisinin resistance.** Regular monitoring and surveillance are critical to identify new foci rapidly and to provide information for containment and prevention activities. WHO recommends that countries endemic for malaria perform routine monitoring of antimalarial drugs at sentinel sites every 24 months in order to detect changes in their therapeutic efficacy (WHO, 2009). An immediate priority is to assess ACT therapeutic efficacy in countries where no studies have been performed in the previous 2 years. Emphasis should be placed on data quality. Regions for which there is evidence of resistance should consider adding further sentinel sites to facilitate early detection of additional foci. In high-risk areas, especially in those with no active sentinel sites, routine surveillance of confirmed malaria cases, deaths and (especially) treatment failures should be strengthened.

3. **Improve access to diagnostics and rational treatment with ACTs.** Increasing access to affordable, quality-assured diagnostics and treatment with ACTs improves patient outcomes and limits opportunities for resistance to both artemisinins and partner drugs (WHO, 2010a). Programmes should include complementary activities to ensure consistent, accurate diagnostic testing, better access to ACTs for confirmed cases, compliance with ACT treatment and removal of oral artemisinin-based monotherapies and substandard and counterfeit drugs. Education and communication campaigns focused on diagnosis and treatment, with messages tailored to patients, providers and retailers, should be a component of these efforts.

4. **Invest in artemisinin resistance-related research.** Research is important to improve understanding of resistance and the ability to manage it. Research in five disciplines should be a priority: laboratory research (e.g. to identify a molecular marker for artemisinin resistance), research and development (e.g. of novel non-artemisinin-based antimalarial combinations), applied and field research (e.g. pilot studies of transmission reduction tools, such as mass screening and treatment or mass drug administration), operational research (e.g. scalable[5] programmes for mobile populations) and mathematical modelling (e.g. of the potential impact of resistance on the malaria burden).

5. **Motivate action and mobilize resources.** Successful implementation of the GPARC will depend on motivating many stakeholders at global, regional and national levels to support or conduct the recommended activities. Additional funding will be required, and leadership and sustained cooperation in the malaria community will be needed to stimulate relevant individuals, organizations and governments to support artemisinin resistance containment and prevention.

The following chapters describe each recommendation in more detail, including the underlying issues and ways in which they might be addressed. Various potential solutions are provided that can be considered by national malaria control programmes and other stakeholders in implementing each recommendation. The solutions described in the GPARC have been prioritized relative to other options based on two criteria: expected relative impact and feasibility.

- Expected relative impact is based on whether a solution addresses the most critical problem or multiple issues simultaneously, has the greatest potential effect on malaria cases and deaths, has an effect within a short time and is sustainable.
- Feasibility is based on the cost and overall resource requirements of the solution (human, financial, operational and scientific), relative simplicity of implementation, the risks and the likelihood of success and the availability of appropriate leader(s), willing partner(s) or support.

[5] In the context of this document, 'scalable' refers to expanding the scope of a tool or programme to reach a larger population or area.

APPLYING RECOMMENDATIONS AT COUNTRY LEVEL

Each solution described is not suitable for every country or area. Given differences in regions and in the level of the threat of artemisinin resistance, each country is expected to evaluate its level of risk and apply the recommendations accordingly to design and implement a containment or prevention programme. To guide implementation, countries should consider the following three classifications:

Tier I Areas for which there is credible evidence of artemisinin resistance;

Tier II Areas with significant inflows of people from tier I areas, including those immediately bordering tier I;

Tier III Areas with no evidence of artemisinin resistance and limited contact with tier I areas.

Chapter 3 describes how the recommendations for management of artemisinin resistance might be applied depending on a country's tier classification. Areas within a country might be classified into different tiers; for example, while most of a country may be tier III, if it shares a border with an area with confirmed or suspected artemisinin resistance, the immediate border region may be classified as tier II. Tier classifications should be re-evaluated regularly. Countries for which there is credible evidence of artemisinin resistance should move rapidly to confirm resistance while simultaneously taking steps to launch containment activities suitable to tier I.

WHO Global Malaria Programme will work with endemic countries to evaluate the accuracy and integrity of data suggesting artemisinin resistance. On the basis of its evaluation of the credibility of the data, WHO Global Malaria Programme, in consultation with its technical expert group on antimalarial drug resistance will recommend whether an area should be reclassified as tier I. Neighbouring countries or countries with significant inflows of people from the affected area should then consider reclassifying their border regions as tier II.

ROLE OF STAKEHOLDERS

Successful implementation of the GPARC recommendations requires coordinated action by stakeholders at multiple levels. Containment and prevention of artemisinin resistance is primarily the responsibility of endemic countries. Many endemic countries will need the support of partners, in the malaria community including multilateral organizations, funding agencies and bilateral donors, nongovernmental organizations, researchers and the private sector. Given the complexity of the required response, stakeholders outside the traditional malaria or public health communities will have to be involved. The roles of specific stakeholders are highlighted in the discussion of each recommendation and priorities by constituency are summarized in chapter 9.

WHO Global Malaria Programme will oversee and coordinate implementation of the GPARC. It will also contribute to execution of the GPARC by providing technical expertise, global surveillance and policy guidance. To fulfill this dual role, WHO Global Malaria Programme has created a new unit dedicated to antimalarial drug resistance. The new unit will receive guidance and oversight from its external technical expert group on antimalarial drug resistance. Given WHO Global Malaria Programme's unique role its priorities will be discussed separately from those of other multilateral organizations in the remainder of the GPARC.

MEASUREMENT AND EVALUATION

Measurement, evaluation and reporting of the GPARC's implementation are critical to successful containment and prevention of artemisinin resistance. Not only does regular reporting and tracking of indicators tend to motivate action, but the availability of timely data is essential for evaluating the evolving threat of artemisinin resistance, tracking progress in managing it, guiding the allocation of limited resources and guiding future containment and prevention activities.

Measurement and evaluation at all levels – global, regional, national and area (tier) – should include regular, formal reporting. Data quality should be a strong focus, as the progress of the GPARC can be assessed only from good data. The tracking and communication of indicators is an essential part of the GPARC implementation. In order to ensure independent, transparent evaluation of the GPARC, WHO Global Malaria Programme will ask the technical expert group to review and evaluate progress and achievements regularly.

The evaluation will be based on a mix of process, outcome and impact indicators. To minimize use of resources, the indicators will be based on data that have already been collected for malaria control and elimination, where possible. Cooperation with the research community could also widen and deepen the pool of information. In some cases, new indicators (such as the number of confirmed treatment failures or the percentage of ACT takers with a confirmed malaria diagnosis) will have to be identified, and new mechanisms will be needed to track and report them.

Some of the key indicators for evaluating implementation of the GPARC are listed in Table 2.

TABLE 2. Indicators for tracking progress in implementation of the GPARC

IMPLEMENTATION AREA	INDICATORS
Malaria burden	• No. of confirmed *P. falciparum* malaria cases (N) • No. of reported treatment failures (N)
Monitoring of drug efficacy	• No. of countries endemic for *P. falciparum* that monitored ACT therapeutic efficacy in the past 24 months (R and G) • No. of countries with confirmed artemisinin resistance (R and G)
Diagnosis	• Percentage of recorded suspected malaria cases tested with RDTs or microscopy (N) • Percentage of patients taking ACTs who have a confirmed parasitological diagnosis (N)
Treatment	• Proportion of confirmed malaria cases receiving ACTs and other antimalarial medicines by sector (N) • Median and average ACT price by sector as reported in outlet surveys (N) • Rate of ACT stock-outs (N)
Prevention	• No. of programmes targeting mobile and migrant populations (N or R) • Proportion of high-risk groups (e.g. forest workers, gem miners, military) with targeted programmes (N or R) • Proportion of targeted population protected by appropriate vector control (N)
Drug manufacture and distribution	• No. of companies marketing monotherapies (R or G) • No. of countries enforcing the ban on monotherapies (N) • Availability of counterfeit or substandard antimalarial drugs as reported in surveys (N) • No. of manufacturing countries committed to addressing illegal drug manufacture (R or G)

G, global; N, national; R, regional.

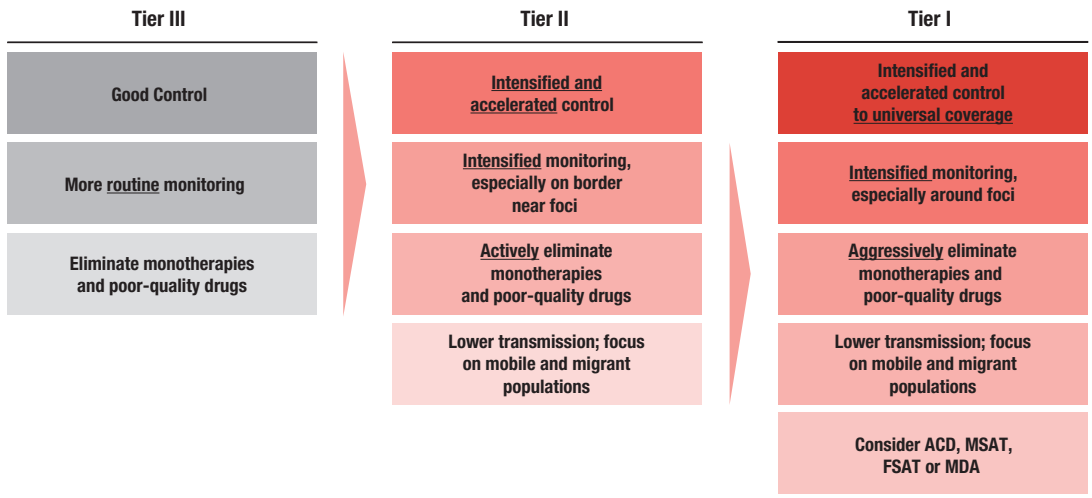
WHO Global Malaria Programme will work with the RBM Monitoring and Evaluation Reference Group to refine the indicators and provide detailed descriptions, including methods of measurement and the assumptions underlying them. Some of the indicators, such as the number of *P. falciparum*-endemic countries in which ACT therapeutic efficacy is monitored, apply only at global or regional level; others, such as the percentage of recorded suspected malaria cases tested by RDTs or microscopy, are relevant only at national level. In some instances, such as the number of reported treatment failures, indicators measured at national level will be applied at the regional or global level to give a view of progress on a broader scale. Additional indicators will probably be identified at national or area level, especially in tier I and II areas where containment is of the highest priority.

3. Summary recommendations by tier

Recommendations will be implemented at varying degrees of intensity and resource commitment, depending on the country or area and the perceived threat of artemisinin resistance. Countries are encouraged to review the evidence for artemisinin resistance within and along their borders in order to evaluate their risk and classify themselves into a tier (as described in chapter 2). Countries can work with WHO regional offices or WHO Global Malaria Programme as needed, especially when new evidence of resistance has emerged. In areas of low or inconsistent transmission, stratification and mapping techniques may be used to target interventions, resulting in more efficient use of resources.

Recommendations by tier are illustrated in figure 5 and summarized below; more detailed recommendations for each tier are given in Table 3 at the end of this chapter.

FIGURE 5. Recommendations by tier



ACD, active case detection; FSAT, focused screening and treatment; MDA, mass drug administration ; MSAT, mass screening and treatment.

TIER I

In areas for which there is credible evidence of artemisinin resistance **an immediate, multifaceted response should be launched.** The goal is to contain and, if feasible, eliminate the resistant parasites. As described in the *Global report on antimalarial drug efficacy and drug resistance, 2000–2010* (section 4.5, Figures 24 and 25), tier I areas included several suspected foci in the Greater Mekong subregion in November 2010. As the situation is evolving, readers should consult the WHO Global Malaria Programme website (http://www.who.int/malaria) for the most recent evidence. Containment activities should continue until malaria or the resistant parasites have been eliminated or it is deemed no longer feasible (e.g. due to significant spread of resistant parasites to other areas). Early data from the ARCE programme in Thailand and Cambodia imply that a containment programme is feasible (see Box 3 for preliminary findings from the ARCE programme). Containment programmes are resource-intensive. Constant efforts are needed to mobilize and maintain sufficient funding, infrastructure and human resources.

BOX 3. ARCE PROGRAMME IN CAMBODIA AND THAILAND

The ARCE programme is an ambitious cross-border strategy for eliminating artemisinin-resistant parasites from the Cambodia–Thailand border. The project was initiated by WHO in close cooperation with the ministries of health of the two countries and many other partners.

It began in 2009 and is still in progress. A full description of its objectives and preliminary results is available in the *Global report on antimalarial drug efficacy and drug resistance*, 2000–2010, section 4.6.
The early results show:

- intensive screening to find and treat hidden cases of resistant malaria in target villages is working;
- vector control tools, like long-lasting insecticide-treated mosquito nets, are effective for reducing transmission in the Greater Mekong subregion;
- village malaria workers can improve the access to diagnosis and treatment of hard-to-reach populations.

Readers are invited to visit the project website for additional information and the final report to be posted at the end of the project (http://www.who.int/malaria/diagnosis_treatment/arcp/en/index.html).

The recommended response for tier I areas is a combination of intensified malaria control and tools for elimination:

- Intensify and accelerate malaria control to reach universal coverage of at-risk populations as soon as possible, including:
  - parasitological diagnosis for all patients with suspected malaria;
  - a full course of quality-assured ACTs plus primaquine for confirmed cases, in compliance with current WHO treatment guidelines (when the risk for glucose 6-phosphate dehydrogenase deficiency is considered low or testing for deficiency is available) (WHO, 2010a); and
  - vector control, as locally appropriate, to lower transmission and minimize the spread of resistant parasites.
- Launch specific activities to contain or eliminate resistant parasites:
  - intensified monitoring of therapeutic efficacy near current foci to track the spread of artemisinin resistance and ensure that the recommended first-line treatments remain effective;
  - education and enforcement to eliminate use of oral artemisinin-based monotherapies and substandard and counterfeit antimalarial medicines;
  - programmes to reach mobile and migrant populations with adequate prevention, diagnosis and treatment; and
  - epidemiological or transmission-reduction tools, which may include mass screening and treatment, focused screening and treatment, active case detection or mass drug administration, in accordance with the latest evidence or guidelines, if and when they become available.

Regular, publicly available reports on progress should be a key component of tier I containment programmes. Reporting should include documentation of current containment activities, achievements (such as rates of coverage with key interventions), challenges and quantitative measures of the evolution of artemisinin resistance. Such measures might include the results of therapeutic efficacy studies, trends in the numbers of confirmed malaria cases and deaths at health facilities and at community level (where community case management programmes exist), malaria positivity rates with diagnostic tests, trends in treatment failure rates and the results of any special surveys conducted in the affected area (either as part of the artemisinin resistance response, such as focused screening and treatment, or for routine purposes, such as a malaria indicator survey). Timely information is critical to guide the global response and, more importantly, to enable national malaria control programmes to adjust their activities appropriately. Formal reporting should be done at least quarterly, and the reports should be distributed to stakeholders and made publicly available. Ongoing reporting requires resources and will depend on close collaboration between countries, funders and WHO.

TIER II

In areas with significant inflows of mobile or migrant populations from tier I areas or shared borders with a tier I area, the main goal is to prevent the emergence of artemisinin resistance, as the movement of populations might spread resistant parasites into tier II areas. As in tier I areas, the recommendations largely mirror those for malaria control. The specific recommendations for tier II areas are:

- Intensify and accelerate malaria control activities, including:
  - parasitological diagnosis for all people suspected of having malaria;
  - a full course of quality-assured ACTs plus primaquine for confirmed cases, in compliance with current WHO treatment guidelines (when the risk for glucose 6-phosphate dehydrogenase deficiency is considered low or testing for deficiency is available) (WHO, 2010a); and
  - vector control, as locally appropriate, to lower transmission, prevent the spread of artemisinin resistance or limit the potential impact of resistance if it were to emerge.
- Implement specific tactics to manage the potential spread of resistant parasites from tier I areas, including programmes to reach mobile and migrant populations, especially those moving between tier I and tier II areas, with effective prevention, diagnosis and treatment.
- Launch activities specific for the prevention of resistance, including:
  - intensified monitoring of therapeutic efficacy to track the spread of artemisinin resistance and ensure that the recommended first-line treatment remains effective; and
  - education and enforcement to eliminate the use of oral artemisinin-based monotherapies and substandard and counterfeit antimalarial medicines.

TIER III

In areas in which there is no evidence of artemisinin resistance and limited contact with tier I areas, the main goal is to prevent the emergence of artemisinin resistance. As artemisinin resistance is a less immediate threat than in other areas, implementation and scaling-up of effective control measures should be continued, including increasing access to parasitological diagnosis for all patients suspected of having malaria, improving access to quality-assured ACTs for confirmed cases and increasing coverage with vector control to limit malaria transmission. In addition, tier III areas should undertake two other components of good control:

- Monitor the therapeutic efficacy of first- and second-line treatments every 24 months, as recommended by WHO. This is an immediate priority for any *P. falciparum*-endemic country with a sufficient number of malaria cases in which studies of the efficacy of ACTs have not been conducted in the past 2 years.
- In areas in which there is extensive use of oral artemisinin-based monotherapies or poor-quality drugs, introduce or enforce actions to eliminate their use.

TABLE 3. Detailed recommendations for tier I, II and III areas

TIER I	RECOMMENDATIONS
Monitoring and surveillance	• Urgently communicate suspicion of a new focus of artemisinin resistance to WHO Global Malaria Programme for review. • When artemisinin resistance is suspected, conduct additional confirmatory studies immediately. • Revitalize regional monitoring networks to complement country monitoring. • Monitor malaria treatment failures regularly; when significant increases are reported, examine the efficacy of current treatments. • Consider increasing the number of sentinel sites in areas surrounding foci of suspected artemisinin resistance as institutional capacity and resources permit.
Diagnostics and treatment: consistent, accurate diagnostic testing	• Accelerate universal coverage in the public sector and the formal private sector delivery channels as rapidly as possible. • Set up pilot programmes to expand access to and use of RDTs in the informal private sector.
Diagnostics and treatment: access to ACTs	• Accelerate efforts to reach 100% coverage with ACTs of confirmed malaria cases in both the public and the private sector delivery channels. • Make sure that programmes include activities to improve access to ACTs in remote areas. • Encourage the manufacture and use of fixed-dose combinations and provide preferential funding for such formulations in areas where the recommended treatment is available as a fixed-dose combination. • Consider adding a single dose of primaquine to ACT treatment for all confirmed cases at or near foci of artemisinin resistance as an antigametocyte to prevent transmission, in compliance with current WHO treatment guidelines (when the risk for glucose-6-phosphate dehydrogenase deficiency is considered low or testing for deficiency is available). Note: WHO currently recommends primaquine for use in low-transmission settings. Primaquine should always be administered in compliance with current WHO recommendations.
Diagnostics and treatment: removal of monotherapies	• Withdraw marketing authorization for oral artemisinin-based monotherapies and remove these medicines from the national Essential Medicines List. • Interrupt importation and distribution of oral artemisinin-based monotherapies. • Commit public providers and retailers to ensure effective withdrawal and increase other activities to encourage removal. • At global level, work with countries and pharmaceutical companies to stop manufacture and export.
Diagnostics and treatment: removal of substandard and counterfeit drugs	• At global level, put pressure on countries in which there are illegal drug manufacturers to stop production and distribution of substandard and counterfeit drugs. • Provide incentives and tools to retailers to identify and remove poor-quality drugs from their facilities. • Conduct quality control screening and field operations to remove poor-quality products.
Diagnostics and treatment: education	• Continue campaigns to educate patients and providers about malaria control, with increased emphasis on the dangers of using oral artemisinin-based monotherapies and poor-quality drugs and the importance of rational use of ACTs (adherence to treatment). Broadcast messages through locally appropriate channels. • Encourage the ministry of health to conduct education campaigns for public health providers on diagnosis and treatment, including the importance of diagnosis before prescribing ACTs and compliance and appropriate use of ACTs. • Launch education campaigns for private retailers on effective diagnosis and treatment, including the risks linked to oral artemisinin-based monotherapies and the regulations banning their marketing and use, tools to detect poor-quality drugs and the importance of confirming malaria with an RDT before treatment with ACTs.
Stop the spread of resistant parasites: preventive measures	• Accelerate efforts to reach 100% coverage with locally appropriate vector control.
Stop the spread of resistant parasites: mobile and migrant populations	• Design programmes to deliver malaria interventions to mobile and migrant populations through a mix of public and private sector delivery channels. • At global level, conduct operational research to identify best practices and scalable* models to reach mobile and migrant populations.
Novel solutions and tools	• Consider the use of mass drug administration, mass screening and treatment, focused screening and treatment or active case detection where there is sufficient local experience in implementation or where policy guidance recommends such measures.

* In the context of this document, 'scalable' means potential upgrading of a programme to expand its scope and reach.

TIER II	RECOMMENDATIONS
Monitoring and surveillance	• For countries in which studies have not been conducted within > 24 months, the immediate priority is to conduct routine studies of ACT efficacy. • Urgently communicate suspicion of a new focus of artemisinin resistance to WHO Global Malaria Programme for review. • When artemisinin resistance is suspected, conduct additional confirmatory studies immediately. • Revitalize regional monitoring networks to complement national activities. • Monitor malaria treatment failures regularly; when significant increases are reported, examine the efficacy of current treatments. • Consider increasing the number of sentinel sites in areas surrounding suspected foci of artemisinin resistance as institutional capacity and resources permit.
Diagnostics and treatment: consistent, accurate diagnostic testing	• Accelerate universal coverage in the public sector and the formal private sector delivery channels as rapidly as possible. • Set up pilot programmes to expand access to and use of RDTs in the informal private sector delivery channels.
Diagnostics and treatment: access to ACTs	• Accelerate efforts to reach 100% coverage with ACTs of confirmed malaria cases in both the public and the private sector delivery channels. • Make sure that programmes include activities to improve access to ACTs in remote areas. • Encourage the manufacture and use of fixed-dose combinations and provide preferential funding for such formulations in areas where the recommended treatment is available as a fixed-dose combination. • Consider adding a single dose of primaquine to ACT treatment for all confirmed cases at or near foci of artemisinin resistance as an antigametocyte to prevent transmission, in compliance with current WHO treatment guidelines (when the risk for glucose-6-phosphate dehydrogenase deficiency is considered low or testing for deficiency is available).
Diagnostics and treatment: removal of monotherapies	• Withdraw marketing authorization for oral artemisinin-based monotherapies, and remove these medicines from the national Essential Medicines List. • Interrupt importation and distribution of oral artemisinin-based monotherapies. • Commit public providers and retailers to ensure effective withdrawal, and increase other activities to encourage removal. • At global level, work with countries and pharmaceutical companies to stop manufacture and export.
Diagnostics and treatment: removal of substandard and counterfeit drugs	• At global level, put pressure on countries in which there are illegal drug manufacturers to stop production and distribution of substandard and counterfeit drugs. • Provide incentives and tools to retailers to identify and remove poor-quality drugs from their facilities. • Conduct quality control screening and field operations to remove poor-quality products.
Diagnostics and treatment: education	• Continue campaigns to educate patients and providers about malaria control, with increased emphasis on the dangers of using oral artemisinin-based monotherapies and poor-quality drugs and the importance of rational use of ACTs (adherence to treatment). Broadcast messages through locally appropriate channels. • Encourage the ministry of health to conduct education campaigns for public health providers on diagnosis and treatment, including the importance of diagnosis before prescribing ACTs and compliance and appropriate use of ACTs. • Launch education campaigns for private retailers on effective diagnosis and treatment, including the risks linked to oral artemisinin-based monotherapies and the regulations banning their marketing and use, tools to detect poor-quality drugs and the importance of confirming malaria with an RDT before treatment with ACTs.
Stop the spread of resistant parasites: preventive measures	• Accelerate efforts to reach 100% coverage with locally appropriate vector control.
Stop the spread of resistant parasites: mobile and migrant populations	• Design programmes to deliver malaria interventions to mobile and migrant populations through a mix of public and private sector channels. • At global level, conduct operational research to identify best practices and scalable* models to reach mobile and migrant populations.

* In the context of this document, 'scalable' means potential upgrading of a programme to expand its scope and reach.

TIER III	RECOMMENDATIONS
Monitoring and surveillance	• For countries in which studies have not been conducted within > 24 months, the immediate priority is to conduct routine studies of ACT efficacy. • Urgently communicate suspicion of a new focus of artemisinin resistance to WHO Global Malaria Programme for review. • When artemisinin resistance is suspected, conduct additional confirmatory studies immediately. • Revitalize regional monitoring networks to complement national activities. • Monitor malaria treatment failures regularly; when significant increases are reported, examine the efficacy of current treatments. • Consider increasing the number of sentinel sites in areas surrounding foci of suspected artemisinin resistance as institutional capacity and resources permit.
Diagnostics and treatment: consistent, accurate diagnostic testing	• Continue current programme to achieve universal coverage.
Diagnostics and treatment: access to ACTs	• Continue current programme to ensure ≥ 80% coverage with ACTs for confirmed cases of malaria, consistent with control and elimination programme. • Encourage the manufacture and use of fixed-dose combinations and provide preferential funding for such formulations in areas where the recommended treatment is available as a fixed-dose combination.
Diagnostics and treatment: removal of monotherapies	• Withdraw marketing authorization for oral artemisinin-based monotherapies, and remove these medicines from the national Essential Medicines List. • Interrupt importation and distribution of oral artemisinin-based monotherapies. • Commit public providers and retailers to ensure effective withdrawal, and increase other activities to encourage removal. • At global level, work with countries and pharmaceutical companies to stop manufacture and export.
Diagnostics and treatment: removal of substandard and counterfeit drugs	• At global level, put pressure on countries in which there are illegal drug manufacturers to stop production and distribution of substandard and counterfeit drugs. • Conduct quality-control screening. If the results indicate a high prevalence of poor-quality drugs: - conduct field operations to remove poor-quality drugs from shelves (consider fines or closing offending shops); and - provide incentives and tools to selected retailers to enable them to identify and remove poor-quality drugs from their facilities.
Diagnostics and treatment: education	• Continue campaigns to educate patients and providers about malaria control, with increased emphasis on the dangers of using oral artemisinin-based monotherapies and poor-quality drugs and the importance of rational use of ACTs (adherence to treatment). Broadcast messages through locally appropriate channels. • Encourage the ministry of health to conduct education campaigns for public health providers on diagnosis and treatment, including the importance of diagnosis before prescribing ACTs and compliance and appropriate use of ACTs. • Launch education campaigns for private retailers on effective diagnosis and treatment, including the risks linked to oral artemisinin-based monotherapies and the regulations banning their marketing and use, tools to detect poor-quality drugs and the importance of confirming malaria with an RDT before treatment with ACTs.
Stop the spread of resistant parasites: preventive measures	• Continue current programme to achieve ≥ 80% coverage with current tools.
Stop the spread of resistant parasites: mobile and migrant populations	• Set up targeted prevention and information programmes at main points of entry for migrants from regions with foci of artemisinin resistance.

4. Stop the spread of resistant parasites

In areas where artemisinin resistance exists, national malaria control programmes and their partners should combine control and elimination programmes to stop the survival and spread of resistant parasites and ultimately contain or eliminate them. In areas with no known resistance, control measures should be used to reduce transmission, lowering the risk that resistant parasites will spread into the area and minimizing the potential public health impact of resistance if it were to emerge. In particular, national malaria control programmes and their partners should use preventive measures to reduce transmission and expand efforts to reach mobile and migrant populations with effective malaria interventions.

4.1 Preventive measures to reduce transmission

Effective preventive measures are important for interrupting malaria transmission and decreasing the number of malaria cases. Vector control methods, including nets and indoor residual spraying, prevent human contact with the vector and reduce the number of vectors (WHO, 2002; WHO, 2006). When these preventive measures are used correctly, the incidence and prevalence of parasite infection and clinical malaria decrease. Unfortunately, many regions endemic for malaria still have low or inconsistent coverage with recommended vector control interventions. In the Greater Mekong subregion, questions were raised about the effectiveness of insecticide-treated nets in some forest settings, but new experience suggests that current tools are effective in reducing transmission in most eco-epidemiological settings in the subregion.[6] The biting behaviour of the most efficient forest malaria vectors *(Anopheles minimus* and *An. dirus)* peaks after 22:00 h. There are some exceptions to this rule, and earlier biting might have implications for the effectiveness of treated nets (Trung et al., 2005).

POTENTIAL SOLUTIONS

The first solution described below, rapid scale-up of vector control measures, is a well-documented component of malaria control. It is emphasized here because it is of particular importance for containing and preventing artemisinin resistance. An additional solution, treating symptomatic patients with an ACT plus primaquine in low-transmission settings at or near foci of artemisinin resistance, is also discussed. While primaquine would be administered as part of a treatment regimen, it is included here because of its transmission-blocking effects.

Epidemiological or transmission-reduction tools, including mass screening and treatment, focused screening and treatment, active case detection and mass drug administration, may also be considered, in accordance with the latest evidence or guidelines. In some areas, enough evidence may exist for a national malaria control programme to choose to implement one of these interventions locally. To date, however, there is insufficient evidence or technical consensus to recommend these interventions for resistance containment; instead, these interventions are discussed further in the research section.

[6] According to interviews conducted by The Boston Consulting Group between May and July 2010.

1. **Rapidly scale-up recommended vector control measures, including personal protection and mosquito abatement measures, in areas for which there is evidence of artemisinin resistance or a high risk for the spread of artemisinin resistance** (see Annex 1 for a description of a case study on the role of vector control in containment on the Cambodia–Thailand border). The scaling-up of preventive measures should include increasing the distribution and improving the maintenance of existing vector control measures (insecticide-treated nets, long-lasting insecticide nets, long-lasting insecticide hammock nets and indoor residual spraying) and ensuring their regular and proper use. Control activities should be intensified at and near areas of suspected or confirmed artemisinin resistance. Potential tactics to accelerate scale-up include use of work-site or employer-based programmes for distribution, channeling more preventive measures through existing distribution networks and expanding and enhancing education activities.
2. **Consider adding primaquine to treatment for confirmed cases, to reduce transmission, at or near foci of artemisinin resistance in low-transmission areas**. Primaquine, a gametocytocidal medicine that can reduce transmission of *P. falciparum*, is recommended by WHO for use in combination with ACTs, particularly in some low-transmission settings and in the context of a pre-elimination or elimination programme (WHO, 2010a). National malaria control programmes should consider treating all confirmed cases of *P. falciparum* with an ACT plus a single dose of primaquine in low-transmission areas at or near artemisinin resistance foci, when the risk for haemolysis due to glucose 6-phosphate dehydrogenase deficiency is considered to be low or when testing for deficiency is feasible.

4.2 Malaria control for mobile and migrant populations

The movement of populations within and between malaria-endemic areas is believed to be a major contributor to the spread of antimalarial resistance. Mobile and migrant populations are a heterogeneous group, which includes individuals and groups who are temporarily moving either within or outside their home country, often for temporary or seasonal work; internally displaced persons moving to new areas due to political conflict or other reasons; and national security forces, which are often clustered near borders. Travellers are also considered part of this group. A variety of approaches to address the needs of these populations is critical to limit the spread of resistant parasites.

For unique reasons, mobile and migrant populations are more likely than other groups to carry and spread resistant parasites: these populations often live and work in areas with high malaria transmission, high human–vector contact and limited access to health services, such as effective malaria prevention, diagnosis and treatment with ACTs. As the presence of some migrants in a country is undocumented, they may mistrust any channel perceived as official, including public health care facilities. In other cases, formal health care services may not be accessible or the cost of care may be prohibitive. As a result, migrant populations are more likely to seek care from unregulated, private vendors, which may increase their risk of exposure to substandard and counterfeit drugs or oral artemisinin-based monotherapy. Once artemisinin resistance has emerged, the frequent movement of these groups makes it difficult to enumerate, track and treat suspected cases and increases the chances that resistance will spread to new areas.

Mobile and migrant populations often cluster near provincial or national borders, and these regions can present unique challenges for implementation and coordination. Neighbouring countries may be unwilling or unable to cooperate because of political tensions, cross-border conflicts, competing priorities, lack of resources or infrastructure or insufficient implementation capacity. These factors may undermine malaria

control activities and humanitarian assistance more broadly. As cross-border collaboration is essential, United Nations agencies play a vital role.

POTENTIAL SOLUTIONS

Given human rights issues are involved with many of mobile and migrant populations, new policy frameworks are needed to find approaches for reaching these at-risk groups. New approaches should be based on public sector delivery when possible but also involve the private sector, including nongovernmental organizations and community-based organizations, as needed. Three potential solutions are:

1. **To reach mobile populations in the short term, strengthen and expand access to preventive and curative services through public and private sector networks.** Existing stationary public sector clinics should be re-equipped to reach their target populations with consistent, accurate diagnostic tests, quality-assured ACTs and vector control tools. Ministries of health, national malaria control programmes and their partners should increase activities to inform populations living close to clinics about the health services available to them. In addition, new stationary clinics should be considered in areas where mobile and migrant populations live and work, if access to health care services and commodities is limited. Private sector networks should also be reinforced. These networks include community-based organizations and local nongovernmental organizations working with private vendors who have created a market for antimalarial medicines and other interventions. The current distribution networks could be supplemented with trained health care providers or distributors to administer RDTs and dispense ACTs. In addition, subsidized interventions could be channelled through these networks to reach target populations without creating separate, new infrastructure. For such activities to be successful, a strict system should be set up to oversee drug resellers, to ensure that free medicines are not sold for profit, which could diminish access to ACTs.
2. **Provide malaria interventions at the work site.** As malaria disproportionately affects workers in specific occupations, such as on rubber plantations and in shipping, another potential solution is to consider malaria an occupational disease and to use the work site as part of the network for distribution of malaria interventions. National malaria control programmes and their partners should collaborate with employers and nongovernmental organizations to increase the distribution of malaria interventions to migrant workers at or near their work sites. The collaboration of employers could be encouraged by demonstrating to employers that it is in their best interests to maintain a healthy workforce in order to increase productivity. Work-site interventions could include on- and off-site diagnostic testing, quality-assured treatment, vector control and surveillance.
3. **Conduct operational research to determine how best to reach mobile and migrant populations with interventions.** The numbers, movements, behaviour and preferences of mobile and migrant populations are not consistently understood by national malaria control programmes and other groups who provide malaria services. Operational research should be conducted to evaluate pilot programmes and identify the best practices for targeting these populations (see section 7.4 for a more detailed discussion of this solution and priorities for research).

5. Increase monitoring and surveillance to evaluate the threat of artemisinin resistance

WHO recommends that countries endemic for malaria routinely monitor the efficacy of antimalarial drugs in order to detect changes in their therapeutic efficacy and guide national treatment policy.[7] Regular monitoring and surveillance are critical for identifying new foci of artemisinin resistance rapidly and guiding containment and prevention activities. Until molecular markers of resistance are identified, measurement and reporting of parasite clearance on day 3 after treatment with ACTs is particularly important, as this is one of the first signals of artemisinin resistance available today.

According to the WHO protocol, national malaria control programmes should evaluate the efficacy of first- and second-line antimalarial drugs at sentinel sites at least once every 24 months (WHO, 2009). The experience gained in the project for confirmation, characterization and containment of artemisinin resistance in Thailand and Cambodia suggests that when more than 10% of patients have detectable parasites on day 3, confirmatory studies should be conducted, which include studies of the efficacy of a 7-day treatment with artesunate. In some instances, it may be appropriate to initiate containment activities when ≥ 3% but < 10% of cases have parasites detectable on day 3 after treatment with an ACT.

Despite the WHO recommendations, many endemic countries do not routinely monitor therapeutic efficacy (Figure 6). Of the 106 endemic countries (92 of which are endemic for *P. falciparum*), 75 have a sufficient burden of malaria to permit routine monitoring of ACT efficacy. As of August 2010, 44 of the 75 countries had not conducted studies in compliance with WHO recommendations within the past 2 years, due to insufficient funding and other resources, extenuating circumstances such as war or natural disaster or a perceived lack of urgency (WHO, 2010c). As a result, understanding of where artemisinin resistance exists is incomplete.

Routine monitoring of the therapeutic efficacy of ACTs is not conducted more widely because of the several constraints (Vestergaard & Ringwald, 2007). These studies can be logistically difficult in some settings, may not be feasible in areas of very low transmission (because of small numbers of malaria cases) and are not always conclusive for detecting resistance, as host factors (e.g. immunity, previous drug intake) can confound the results. Even when therapeutic efficacy studies are conducted, the results are often not made available rapidly, especially when studies are conducted outside of the national malaria control programme.

POTENTIAL SOLUTIONS

National malaria control programmes and their partners should consider:

1. **As an immediate priority, monitor the therapeutic efficacy of ACTs if a study has not been performed within the past 2 years.** To obtain a comprehensive understanding of where parasites are resistant to artemisinins, the efficacy of ACTs must be known in all endemic countries.[8] For the 44 countries in which studies have not been conducted in compliance with WHO guidelines since the

[7] Although therapeutic efficacy monitoring should be a routine activity of national malaria control programmes, rather than individual or isolated research projects, because of the complexity of the protocol, monitoring is conducted through what are referred to as therapeutic efficacy studies (also called in vivo studies). Accordingly, the individual activites are referred to as 'studies', even though monitoring is an ongoing, routine activity.

[8] The phrases 'all endemic countries' and 'all endemic regions' used in the context of routine monitoring refer to countries or regions with sufficient numbers of malaria cases to monitor therapeutic efficacy.

end of 2007, an immediate priority is to determine the efficacy of currently used first- and second-line drugs. The studies should be performed in compliance with the most recent WHO protocol, with a strong emphasis on data quality (WHO, 2009). A financial commitment from donors is required to ensure the sustainability of therapeutic efficacy studies in endemic countries.

2. **Revitalize subregional networks to support national monitoring.** To complement monitoring activities in countries, subregional monitoring networks should be revitalized or redesigned. Networks can provide important benefits, including encouragement and incentives for countries to conduct regular monitoring, identification of subregional trends, coordination of a subregional response when required and sharing data regarding border areas. If subregional networks are to play a significant role in responding to the threat of artemisinin resistance, sustainable financing and stable network management structures are needed (see Annex 2 for a description of subregional monitoring networks).

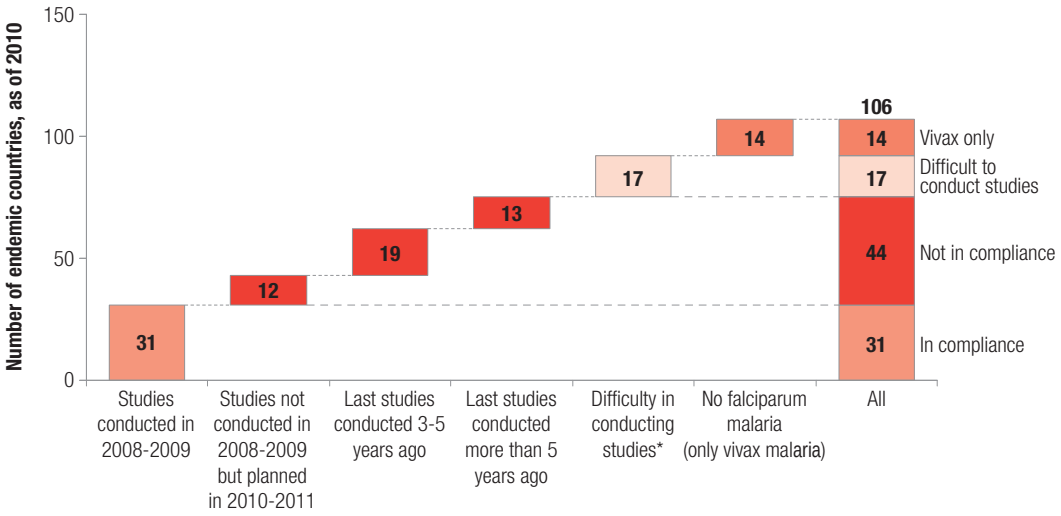
3. **Urgently communicate suspicion of new foci of artemisinin resistance.** Any information suggesting new foci of artemisinin resistance should be communicated immediately to WHO Global Malaria Programme, which will work with scientists, including the technical expert group on antimalarial drug resistance, to evaluate the accuracy and integrity of the data. If resistance is confirmed, the data should also be shared with relevant policy-makers and global malaria partners for a timely, well-coordinated response. Current data dissemination systems should be enhanced so that all stakeholders are kept up to date as the situation evolves. This recommendation applies not only to national malaria control programmes which routinely monitor the efficacy of ACTs, but also to researchers and pharmaceutical companies involved in studies on the therapeutic efficacy of ACTs or artesunate.

4. **When evidence of artemisinin resistance already exists, consider adding new sentinel sites near foci of artemisinin resistance.** As it is difficult to extrapolate information on resistance from an isolated focus to nearby areas, adding new sentinel sites near areas for which there is already evidence of artemisinin resistance can clarify whether and where artemisinin resistance has spread. National malaria control programmes should work with WHO Global Malaria Programme and other experts to determine whether additional sites would be beneficial in their context. If new sites are to be added, the malaria control programme should coordinate and oversee their establishment and the conduct of studies but may involve other partners as needed.

5. **Strengthen routine surveillance of malaria.** In high-risk areas, and especially in areas with no active sentinel sites, national malaria control programmes should consider strengthening routine surveillance of confirmed malaria cases and deaths, and especially treatment failures. The programmes should introduce a mechanism whereby health care providers can identify and report treatment failures. Although it may be difficult to obtain such data from private providers, this is important in areas where a large proportion of the population seeks care privately. When regular surveillance indicates an increased number of treatment failures or increases in the numbers of cases or deaths from malaria, additional studies should be conducted to rule out artemisinin resistance as the cause. Increases in treatment failures and in morbidity or mortality are late indicators of resistance[9] but may be useful when therapeutic efficacy is not routinely monitored.

[9] Increases in morbidity and mortality can be due to many factors, only one of which is the emergence or spread of artemisinin resistance. By the time artemisinin resistance has led to a noticeable increase in morbidity or mortality, resistance is probably already well entrenched locally, and the extent of geographical spread would not be known immediately. Thus, increases in morbidity and mortality provide only a very late indicator of resistance.

FIGURE 6. Status of therapeutic efficacy monitoring in 106 countries endemic for malaria



* Very small number of cases makes it difficult to conduct studies in these countries.
Source: WHO Global Malaria Programme database on antimalarial therapeutic efficacy monitoring by country (accessed August 2010).

6. Improve access to diagnostics and artemisinin-based combination therapies

Improving access to affordable, quality-assured diagnostic testing and treatment with ACTs improves patient outcomes and limits the opportunities for emergence of resistance to both artemisinins and partner drugs. Programmes should have a multifaceted approach that improves access to both consistent, accurate diagnostic testing and quality-assured ACTs for confirmed cases, while removing oral artemisinin-based monotherapies and substandard or counterfeit drugs from the market. Each of these issues requires understanding and education of and dialogue with patients, providers and retailers. The proposed solutions for each issue are complementary and, wherever possible, should be coordinated.

6.1 Consistent, accurate diagnostic testing

Confirmation of malaria by parasitological diagnosis is important to prevent unnecessary overuse of antimalarial medicines and limit the opportunities for emergence of resistance to both artemisinins and partner drugs. Administration of an ACT to a person who does not have malaria does not cause drug resistance; the problem arises when that person is later exposed to malaria. If this occurs relatively soon after the ACT is taken, the presence of the two drugs makes selection of a resistant parasite unlikely; if exposure occurs later, when only the partner drug may be present in the blood at a subtherapeutic level, resistant parasites may be selected. High-transmission areas are of greatest concern, because people in these areas are more likely to be bitten by an infected mosquito at a time when only the partner drug is present in blood. If the partner drug becomes less effective or ineffective, it no longer provides adequate protection for the artemisinin derivative in the ACT. As a result, artemisinin and its derivatives may be threatened.

ACTs are frequently used to treat causes of fever other than malaria. It has been shown that a median of 78% of patients treated for malaria in Africa may not actually have malaria, and this proportion has increased over time (d'Acremont, Lengeler & Genton, 2010). As malaria control programmes continue to reduce both malaria transmission and malaria burden, the proportion of fevers due to malaria will continue to decrease.Without appropriate diagnosis, more ACTs will be wasted on non-malarial febrile illnesses, potentially increasing the risk for selecting resistant parasites. To reduce the number of patients without malaria taking ACTs, all suspected cases of malaria should be diagnosed parasitologically before treatment, as recommended by WHO (WHO, 2010a).

Diagnostic testing also plays a critical role in ascertaining possible cases of antimalarial resistance. Patients who fail to improve clinically or who improve but have a subsequent relapse should return to a health care provider for re-evaluation. Microscopy should be used to determine if parasitaemia is still present, as RDTs may give positive results for varying lengths of time, even after successful treatment. If a pattern of increasing therapeutic failures emerges, follow-up studies should be conducted to investigate the cause.

Although the availability and use of parasitological diagnosis is increasing, there are clear opportunities for improvement (see Annex 3 for a case study on the use of parasitological diagnosis). By 2009, about 35% of suspected malaria cases in endemic countries of the WHO African Region were tested by microscopy or an RDT (WHO, 2010b). Although this represents a significant increase since 2004, most suspected cases in these endemic countries are still not tested, even in the public sector. Various challenges preclude more widespread adoption of diagnostics, including problems of distribution (Renshaw et al., 2009), and variability in the

quality and performance of RDTs, including sensitivity, specificity, heat stability and longevity (WHO, 2010d). Furthermore, some providers and patients are still unaware of the harm associated with treating cases without malaria with ACTs, and in some settings patients with negative results from a diagnostic test still receive and take antimalarial medicines (Hamer et al., 2007; Reyburn et al., 2007; J. Cohen, unpublished data).

Measures are being taken to address these challenges. Recent successes include improvement of the supply chain to ensure that high-quality RDTs are available where and when needed; testing of RDT products and lots by WHO, the Special Programme for Research and Training in Tropical Diseases, the Centers for Disease Control and Prevention and the Foundation for Innovative New Diagnostics; and intensive provider training programmes, often accompanied by supervision. There are also efforts under way to improve provider and patient compliance with the results of testing.[10] In the United Republic of Tanzania, proper provider training and regular supervision were shown to encourage compliance with testing results (d'Acremont, personal communication). In Ghana, in health facilities with no previous access to malaria diagnostic testing, the introduction of RDTs led to a significant reduction in overprescription of antimalarial medicines (Ansah et al., 2010). Nevertheless, ensuring the use of RDTs and compliance with the results in the informal private sector is likely to be a tremendous challenge. For example, in a study in Kenya, there was demand for RDTs in the private sector at low prices, but access to RDTs only modestly improved targeting of ACTs because most patients with negative test results purchased ACTs anyway (J. Cohen, unpublished data).

POTENTIAL SOLUTIONS

Four parallel activities are proposed to encourage the use of parasitological diagnosis and compliance with the results.

1. **Accelerate universal coverage with parasitological diagnosis in the public sector and the formal private sector.**[11] In order to prevent overuse of ACTs, universal access and use of parasitological diagnosis in public and formal private sector health facilities should be achieved as soon as possible. Access can be increased by strengthening the distribution networks of RDTs, improving supply chain management, improving quality assurance and strengthening community health services. Use might be increased by more training of health care workers in microscopy and use of RDTs and introducing quality assurance systems to verify that the tests are administered regularly and properly. Donors should consider increasing funding for diagnostics and the systems needed to implement and properly maintain programmes for universal diagnostic testing.
2. **Continue to test new approaches to increase access to and use of parasitological diagnosis in the informal private sector.**[12] More operational research and pilot tests are needed to identify the most effective strategies for increasing use of diagnostics in the informal private sector. For example, more data are required to understand how the cost of RDTs influences use and whether subsidizing RDTs at country level or globally is feasible.
3. **Continue to improve the quality of RDTs.** Activities to ensure the quality, consistency and reliability of RDTs and their supply chains should continue, in collaboration with RDT manufacturers. For example, the RDT product testing and lot-quality testing programmes conducted by WHO, the Special Programme for Research and Training in Tropical Diseases, the Centers for Disease Control and Prevention and the Foundation for Innovative New Diagnostics provide data to endemic countries to guide their purchase of high-quality diagnostics and encourage manufacturers to improve the quality of their products (WHO, 2010d).

[10] According to interviews conducted by The Boston Consulting Group between May and July 2010.

[11] The 'formal private sector' is the regulated part of the market.

[12] The 'informal private sector' is the unregulated (unregistered premises or practitioner) part of the market.

4. **Intensify efforts to educate providers and patients about the importance of diagnostic testing.** To convince providers and patients of the importance of diagnostic testing before treatment, current education and training initiatives should be expanded or reviewed, with robust monitoring and evaluation to ensure effectiveness. At community level, patients should be informed about the importance of timely, accurate diagnosis of malaria and of not taking ACTs without a confirmed parasitological diagnosis. Additional training, supervision and access to the necessary commodities are also important to enable health care providers to diagnose and treat patients when the RDT is negative.

6.2 Access to affordable, quality-assured artemisinin-based combination therapy

ACTs are an effective, rapid treatment for *P. falciparum* malaria. When manufactured and administered in adherence with treatment guidelines, combination therapies are not only more effective than monotherapies, but the mutual protection provided by two drugs reduces the chance that resistance will emerge. A 3-day course of a recommended ACT generally results in rapid clearance of parasites and resolution of symptoms. In addition, the artemisinin component of the combination reduces gametocyte carriage, thus reducing malaria transmission. Because ACTs have multiple advantages over other antimalarial treatments, WHO recommends ACTs as first-line treatment for confirmed cases of uncomplicated *P. falciparum* malaria (WHO, 2010a). The current list of recommended ACTs is given in the WHO guidelines for treatment of malaria, which is available at: http://www.who.int/malaria/publications/atoz/9789241547925/en/index.html. The choice of ACT depends on local data on the sensitivity of *P. falciparum* to different ACTs.

Despite the availability of WHO guidelines for treatment and the fact that most endemic countries have adopted ACTs as first-line treatment, non-artemisinin-based therapies and oral artemisinin-based monotherapies are still the dominant forms of treatment in many malaria-endemic countries, especially in the private sector. Initiatives to expand access to ACTs face significant challenges in both the public and the private sector. In the public sector, challenges include recurrent stock-outs of ACTs due to procurement and supply chain difficulties and problems of geographical access to public health facilities. In the private sector, challenges include the fact that ACTs are more expensive than other, readily available antimalarial medicines; poor regulation and enforcement mechanisms; and lack of access by remote and mobile populations.

While access to ACTs remains inconsistent in endemic countries, in areas where a concerted effort is made to adhere to WHO guidelines for treatment and adequate resources are committed, it is possible to improve ACT access significantly (see Annex 4 for the availability of ACTs in selected endemic countries).

POTENTIAL SOLUTIONS

National malaria control programmes and their partners should consider the activities described below to improve access to affordable, quality-assured ACTs for confirmed cases of malaria. Patients should be encouraged to seek care in the public or the formal private sector whenever possible. As all patients may not have access to these facilities and many people turn to the informal private sector for care, solutions should be identified to reach informal private sector outlets.

1. **Ensure consistent availability of quality-assured ACTs in the public sector by improved financing, procurement and distribution.** Endemic countries should secure sufficient funding to be able to provide a consistent supply of ACTs to public health facilities, including increased national funding where possible. In addition, national malaria control programmes and their partners should improve management of the supply chain, including demand forecasting, procurement and distribution, to maintain appropriate stocks of ACTs at points of care. Consistent diagnostic testing can help reduce the number of ACTs used to treat cases without malaria and improve the accuracy of demand forecasting.

2. **Make sure that quality-assured ACTs are available and affordable in the private sector.** Countries endemic for malaria and their partners should continue to seek new mechanisms for ensuring the availability of affordable, quality-assured ACTs in the private sector (see Annex 1 for a case study on providing subsidized ACTs to the private sector in Cambodia). The use of incentives to encourage private sector outlets to comply with diagnosis and treatment regulations and guidelines should be evaluated. Lessons from the pilot study being conducted by the Affordable Medicines Facility – malaria in eight countries should be incorporated as they are reported (Box 4). The availability of quality-assured ACTs in the private sector should be tracked to identify gaps and better understand the requirements for universal access.

3. **Improve access to affordable, quality-assured ACTs in remote areas, primarily through community-based case management.** Little is known about how best to reach people living in remote areas with malaria control interventions, and research is needed to test new approaches. The findings from such initiatives should be the basis for new programmes, which might incorporate a 'treatment-seeking patient' strategy or incorporate innovative means of communication and treatment.[13] Such approaches should be explored for mobile, migrant and static minorities and for groups such as the military and police. The important role of community health workers in improving access for hard-to-reach populations should be recognized and encouraged. The 'village malaria worker' programme implemented in Cambodia is an example of an innovative programme already under way (see Annex 1 for a case study on a village malaria workers programme).

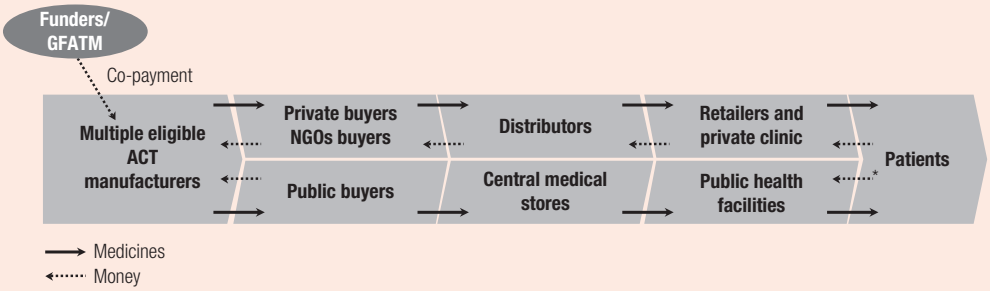
4. **Improve compliance with treatment with ACTs by encouraging the manufacture and use of fixed-dose combinations and through education campaigns.** In order to improve compliance with treatment guidelines (e.g. to reduce the tendency of some patients to take only the artemisinin portion of a combined treatment or not to complete the 3-day course), the manufacture, marketing and use of fixed-dose combinations should be strongly encouraged. National drug regulatory authorities and ministers of endemic countries should be encouraged to register fixed-dose combination ACTs as soon as possible. In both the public and the private sector, priority should be given to the procurement and distribution of fixed-dose combination formulations in areas where the recommended treatment is available in this form (WHO, 2010a).[14] When the recommended treatment is available in a fixed-dose combination, funders should consider giving preference to such formulations. National malaria control programmes and their partners should also consider behavioural change interventions for patients and providers, to improve compliance, including behaviour change communication or information education communication. To support these programmes, additional evidence is needed about people's understanding of drugs and the best way to disseminate messages.

[13] According to interviews conducted by The Boston Consulting Group between May and July 2010.

[14] Fixed-dose combination formulations are now available for all recommended ACTs except artesunate plus sulfadoxine–pyrimethamine.

BOX 4. THE AFFORDABLE MEDICINES FACILITY–MALARIA

The Affordable Medicines Facility – malaria, is a financing mechanism to expand access to ACTs and displace less effective or undesirable monotherapies, including oral artemisinin-based monotherapies. The Affordable Medicines Facility – malaria benefits buyers from all sectors and it has three elements: price reductions through negotiations with ACT manufacturers, a buyer subsidy through a 'co-payment' at the top of the supply chain, and supporting interventions to promote appropriate use of ACTs. It is hosted and managed by the GFATM.



* with or without payments, depending on country policy and practice.
NGOs, nongovernmental organizations.

Potential benefits:

- Increases affordability and use of first-line ACTs for malaria cases, thereby saving more lives than would be the case without the Affordable Medicines Facility – malaria;
- Displaces oral artemisinin-based monotherapies, thus reducing risk of artemisinin resistance below what might happen without Affordable Medicines Facility – malaria;
- Through implementation research, provides opportunities to learn how the private sector can be used to expand access to health technologies, including rapid diagnostic tests.

Potential risks:

- Some distributors in the supply chain may capture much of the subsidy, reducing the benefits to some patients;
- Without universal use of, and compliance with, diagnostic tests in Affordable Medicines Facility – malaria phase 1, it increases the use of first-line ACTs for non-malarial febrile illnesses.

6.3 Removal of oral artemisinin-based monotherapies

Unlike ACTs, which require only 3 days to result in high cure rates, oral artemisinin-based monotherapies require 7 days for comparable efficacy, and many patients stop taking them after only a few days, when their symptoms have diminished significantly. When adherence is incomplete, parasites in a patient's blood are exposed to a subcurative dose; while the most sensitive parasites are eliminated, the more resistant ones can survive and be transmitted to others. As a result, the use of oral artemisinin-based monotherapies may hasten the spread of artemisinin resistance.

WHO has worked with pharmaceutical companies to halt the production of oral artemisinin-based monotherapies since 2005 (see Annex 5 for a description of WHO's activities in removing oral artemisinin-based monotherapies). Initially, 76 companies were known to be producing and marketing these formulations, and this number has decreased to 43 (see Annex 5 for a list of areas of the world in which oral artemisinin-based monotherapies are produced). While these results are encouraging, it will be difficult to influence the remaining small producers, which continue to exploit the niche markets created by the withdrawal of big pharmaceutical companies. The continued manufacture and distribution of oral artemisinin-based monotherapies and poor regulation of drug markets in many countries endemic for malaria contribute to persistent use of these drugs. Despite the work of WHO, the RBM Partnership and other stakeholders, as

of December 2010, the national drug regulatory authorities in 25 endemic countries still allowed marketing of oral artemisinin-based monotherapies for use in the private sector (see Annex 5 for a list of countries that still allow marketing of oral artemisinin-based monotherapies for use in the private sector and Annex 1 for a description of the successful interruption of the importation and sales of oral artemisinin-based monotherapies in Cambodia). No data are available on the number of treatment courses of oral artemisinin-based monotherapy produced throughout the world annually.

POTENTIAL SOLUTIONS

Four parallel efforts are proposed to reduce the production and marketing of oral artemisinin-based monotherapies.

1. **Work with governments and manufacturers to stop production, marketing and export of oral artemisinin-based monotherapies through targeted regulatory interventions.** National and municipal governments should withdraw manufacturing and export licenses and marketing authorization for oral artemisinin-based monotherapies. The initiatives could include taking punitive action against companies that fail to cease manufacture, marketing or export; increasing the capacity of national drug regulatory authorities and making them accountable for effectively withdrawing manufacturing licenses; and involving local police and drug inspectors in enforcement. In parallel, the 43 known pharmaceutical companies that still provide oral artemisinin-based monotherapies to the private sector should be engaged. This will require a communication campaign for shareholders or owners about the risks associated with these formulations, negotiating a deadline with manufacturers by which they will stop manufacture or export of such products, determining what assistance companies need to stop production and perhaps change to production of ACTs and supporting companies in developing plans to implement changes. As the production of oral artemisinin-based monotherapies decreases, WHO will work with selected companies to ensure the availability of prequalified oral artemisinin-based tablets for specific, carefully controlled uses, including therapeutic efficacy studies and the treatment of severe malaria.
2. **Interrupt importation and wholesale buying of oral artemisinin-based monotherapies.** Malaria-endemic countries should implement and enforce regulations to halt the importation and wholesale buying of oral artemisinin-based monotherapies by the private sector. Regulations could include stopping import licenses and suspending new marketing authorization for finished products; withdrawing marketing authorization and manufacturing licenses for finished products; regulating re-packaging and re-branding by domestic companies; removing oral artemisinin-based monotherapies from national lists of registered drugs; and ensuring that national drug regulatory authorities, the police and other relevant government agencies and departments enforce removal of oral artemisinin-based monotherapies from the country. In many cases, implementation will require investment to strengthen drug regulatory authorities.
3. **Actively engage retailers and other providers to ensure effective withdrawal of monotherapies.** Retailers and other providers should be informed about the risks caused by oral artemisinin-based monotherapies, how the emergence of resistance could affect outcomes in patients, especially children and about the measures taken to halt marketing and use and the penalties that shops might incur if they continue to sell these products. Assuming affordable ACTs are available through private sector delivery channels, initiatives should be taken to track, report on and remove oral artemisinin-based monotherapies. Activities may include: implementing routine field investigations and reporting the findings to national drug regulatory authorities so they can take follow-up action if needed; identifying and reporting the sources of such products to WHO

and relevant enforcement bodies; certifying and accrediting retailers that sell only quality-assured ACTs; and fining retailers that continue to sell oral artemisinin-based monotherapies and other non-approved antimalarial medicines.

4. **Inform patients about the risks associated with taking oral artemisinin-based monotherapies in order to reduce demand.** An education campaign is needed for patients and caregivers in endemic countries to explain clearly the potential harm of taking oral artemisinin-based monotherapies and the potential impact of antimalarial resistance on outcomes, especially for children. Patients should be educated to take only recommended drugs, instructed on how to identify quality-assured ACTs and made aware of the importance of completing the prescribed treatment.

6.4 Removal of substandard and counterfeit drugs

Because substandard and counterfeit antimalarial medicines contain insufficient levels of artemisinin derivatives, they threaten the health of patients and may lead to the development and spread of artemisinin resistance, as regular use of such products may allow resistant parasites to survive and multiply.

'Substandard drugs' are medicines that do not meet the correct scientific specifications for composition and ingredients and are consequently ineffective and potentially dangerous for the patient. 'Counterfeit drugs' are a category of substandard drugs that are deliberately and fraudulently mislabelled for profit-making purposes. Counterfeits may contain only traces of active ingredients or no active ingredient at all (WHO, 2010e).

Substandard antimalarial medicines are prevalent in many malaria-endemic countries. In a study in Senegal in 2008, for example, 44% of 62 drug samples from the public, private and informal sectors did not meet requirements in a full quality control test (United States Pharmacopeia Drug Quality and Information Program, 2010). Counterfeit drugs are also a significant problem in many endemic countries. In a study conducted between 1999 and 2006 in South-East Asia, 50% of 391 samples of medicines marked as artesunate were found to be counterfeit after careful examination of the packaging and drug quality testing (Newton et al., 2008). Modern chemical, mineralogical and biological techniques and analyses of packaging can help inspectors to determine the origin of drugs, and concerted and coordinated efforts can achieve notable results in removing poor-quality drugs from the market (see Annex 1 for a description of a successful initiative in Cambodia to remove poor-quality drugs).

POTENTIAL SOLUTIONS

Four initiatives are proposed to reduce the production and use of poor-quality drugs.

1. **Survey the quality of drugs to guide policy recommendations and regulations.** In countries where the prevalence of substandard and counterfeit drugs is not known, countries should consider initiating targeted drug screening at representative sites. To complement these surveys, countries should set up educational campaigns to inform providers and shop owners about regulatory policies and should collect random samples from drug retailers. To support drug screening, new tools are needed to help enforcement agencies, retailers and consumers identify substandard, counterfeit and unregistered drugs (Phanouvong & Blum, 2004). Research is also needed to develop simple, sensitive tools and analytical methods for rapid use in the field.

2. **Take immediate regulatory action to stop the manufacture and wholesale purchase of counterfeit drugs**. In order to stop the manufacture, importation and distribution of counterfeit antimalarial medicines, their origin must be known. If the source is unknown, efforts should be made to trace counterfeit drugs back to their site of production, starting with the retail outlet at which it was purchased. Pressure should be placed on countries with illegal drug manufacturing facilities to stop production and better regulate exportation and distribution. For these efforts to be effective there must be close coordination among health professionals, distributors, health authorities, drug regulatory authorities, the police and Interpol, and customs departments. The WHO International Medical Products Anti-counterfeiting Taskforce[15] could work with Interpol and others to share data on sources of poor quality drugs in various countries in order to shut down illegal manufacturing facilities.[16]

3. **Provide incentives and tools to help national drug regulatory authorities, providers and retailers to identify and remove substandard drugs from the market.** On the basis of the results of surveys to identify substandard drugs, countries should establish regular monitoring of the quality of drugs in both the formal and the informal market and set up enforcement mechanisms to enable drug inspectors to confiscate and destroy medicines found to be substandard. The capacity of national drug regulatory authorities to deal with substandard drugs should be improved urgently. Innovative mechanisms should be found and evaluated to help providers and retailers in verifying the quality and authenticity of ACTs before they buy them, including working with manufacturers to incorporate registration numbers, bar codes or coloured signals that are not visible to the naked eye on packaging; an easy, rapid test for the authenticity of a product; and teaching providers and retailers to detect substandard drugs. To help patients purchase quality-assured ACTs, countries might consider accrediting 'approved' retailers or using text messaging (short message service, or SMS) to validate the authenticity and quality of a drug.[17]

4. **Educate patients on the importance of using quality-assured medicines.** Because consumers may find it difficult to distinguish between quality-assured ACTs and substandard or sophisticated counterfeit drugs, education campaigns should focus on alerting patients to unreliable sources of medicines in the private sector and encouraging them to seek treatment in accredited health facilities.[18] Where applicable, campaigns should encourage patients to seek care in the public sector; if this is not possible, patients should be encouraged to use certified sellers of antimalarial drugs to minimize the risk of purchasing a poor-quality drug.

[15] The International Medical Products Anti-counterfeiting Taskforce was created in 2006 by WHO to raise awareness and encourage action against fake medicines. Its aim is to build coordinated networks in and between countries to halt the production, trade and sale of counterfeit medicines and to protect people from buying and taking them.

[16] According to interviews conducted by The Boston Consulting Group between May and July 2010 and the terms of reference of the International Medical Products Anti-counterfeiting Taskforce.

[17] According to interviews conducted by The Boston Consulting Group between May and July 2010.

[18] According to interviews conducted by The Boston Consulting Group between May and July 2010.

7. Invest in research on artemisinin resistance

As so little is known about the development and spread of artemisinin resistance, the research community has a critical role to play in understanding and containing the threat. Many of the priorities already identified for research in malaria control and elimination will be relevant, but they will not be sufficient, and additional initiatives are needed in the five areas listed in Table 4. Some of the research needs in each of these categories are described in the following section, which is not, however, intended to be a comprehensive research agenda.

TABLE 4. Categories of research required on artemisinin resistance

CATEGORY	GPARC PRIORITY
Laboratory research	To allow faster detection of resistance
Research and development	To ensure the availability of new drugs to replace those that become ineffective because of resistance
Applied and field research	To determine whether new tools or existing tools applied or combined in novel ways can be used to contain or prevent artemisinin resistance
Operational research	To improve the effectiveness in the field of current and new tools, interventions and programmes for combating artemisinin resistance
Mathematical modelling	To predict the potential spread and effects of artemisinin resistance and the effects of interventions to contain or prevent it

7.1 Laboratory research

There is currently no molecular marker or specific in vitro test to identify artemisinin resistance, and national malaria control programmes and others rely on therapeutic efficacy studies, which are time-consuming and costly, to detect and confirm resistance. As screening for molecular markers could be done more easily in more settings than in vitro testing, identification of a molecular marker is a high priority. The availability of such a marker would dramatically improve the speed and accuracy of detection of artemisinin resistance by allowing more efficient population-level screening. Testing for molecular markers is logistically feasible, because samples are easily obtained, transported and stored, and national malaria control programmes, in conjunction with research institutions, could use these tests routinely in a large population. If initial screening showed evidence of artemisinin resistance, programmes could then conduct therapeutic efficacy studies to confirm it.

Laboratory research on the mechanism of artemisinin resistance is another priority. Although several groups are studying this topic, why and how resistance develops and what factors cause it to spread remain largely unknown. Understanding the molecular basis of artemisinin resistance and the associated genotypes and phenotypes will provide insight into the mechanism and may help to predict the spread of resistant parasites. It might also indicate whether the resistance will affect all artemisinin derivatives or is drug-specific. Research to identify other factors that affect artemisinin resistance, such as transmission intensity and drug use patterns, could also help to identify areas in which artemisinin resistance might emerge or spread.

To answer these research questions, new approaches to collaboration and data-sharing are needed. Initiatives are already under way to improve collaboration in laboratory research. For instance, the World Wide Antimalarial Resistance Network has set up the Artemisinin Resistance Marker Platform, a collaborative effort to identify genetic loci linked to delayed parasite clearance time and to validate candidate markers of resistance emerging from these and other studies (http://www.wwarn.org). Another example is the Infectious Disease Initiative of the Broad Institute, which brings together genomics scientists studying the mechanisms behind malaria, who apply this knowledge to its prevention and treatment (http://www.broadinstitute.org/science/programs/infectious-disease-initiative/infectious-disease-initiative).

7.2 Research and development

Research and development on artemisinin resistance should focus first on finding new, non-artemisinin-based antimalarial medicines. New transmission-blocking antimalarial medicines and new diagnostics are also needed.

NEW ANTIMALARIAL MEDICINES

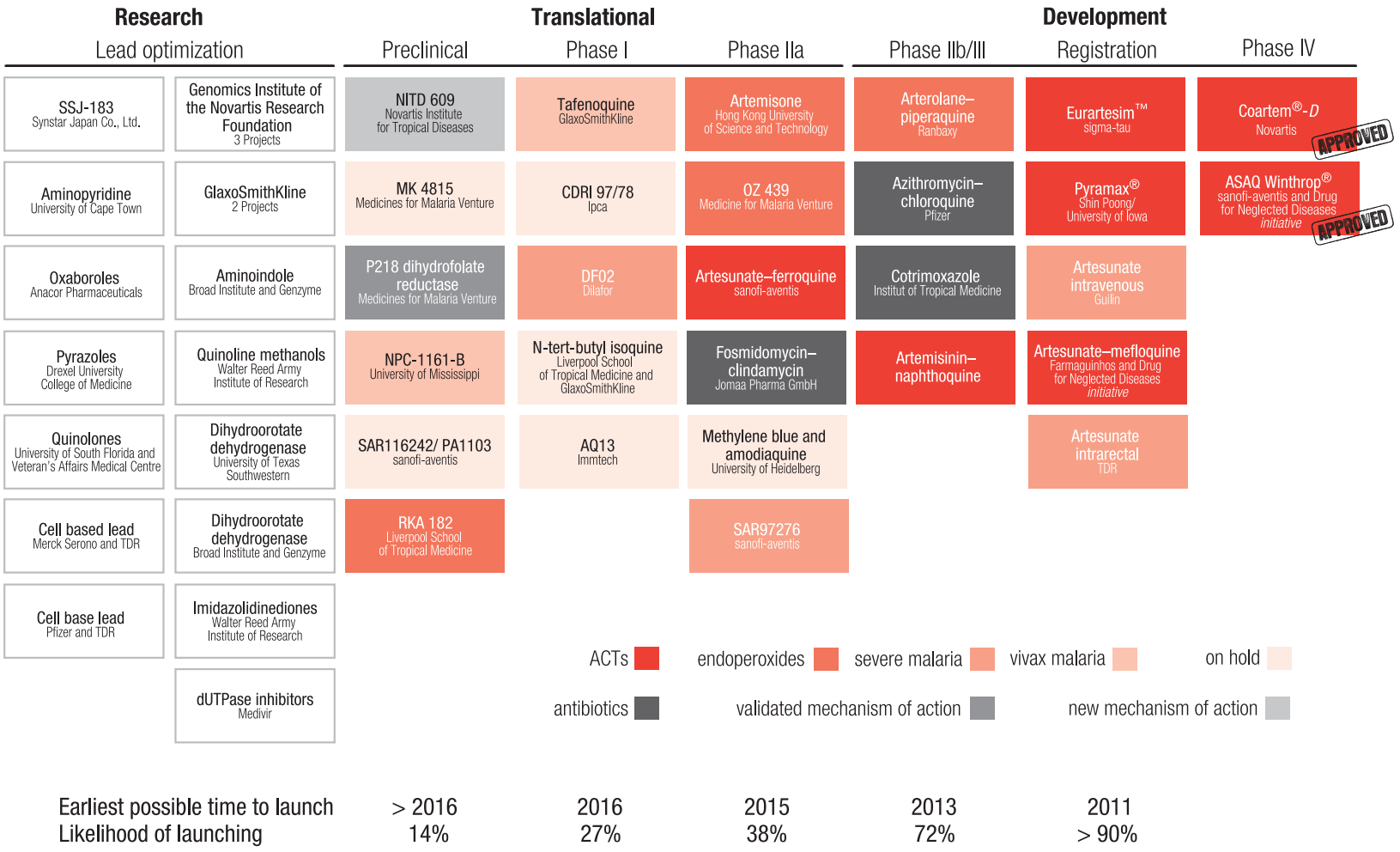
The emergence and potential spread of resistance to artemisinins means that artemisinins, and consequently ACTs, could be lost as an effective treatment for *P. falciparum* malaria. At present, no other antimalarial medicines are available that offer the same level of efficacy and tolerability as ACTs, and there are few promising candidates in the pipeline. The ideal drug would be a co-formulated combination, suitable for mass administration and administered at a single encounter, which offers radical cure of malaria caused by all life-cycle stages of all five human malaria species. Such a 'single exposure radical cure and prophylaxis' drug would eventually allow malaria elimination and eradication (The malERA Consultative Group on Drugs, 2011). In the absence of such a drug, investment in research and development of other, safe, effective, non-artemisinin alternatives is critical.

Currently, fewer than 30 antimalarial drugs are under development from the preclinical stage to phase IV, and an additional 15 candidate drugs are in early stages of research (Figure 7). Much of the development is coordinated by the Medicines for Malaria Venture. Only a limited number of the drugs in development are potential alternatives to artemisinin-based therapies. Six candidates are endoperoxides or synthetic artemisinins, including arterolane/OZ 277 (phase IIb/III) and OZ 439 (phase IIa). It is not known whether synthetic artemisinins will be effective against artemisinin-resistant parasites. If endoperoxides prove to be ineffective, antibiotic combinations are the next most promising candidates. Clindamycin–fosmidomycin is in phase II, and another antibiotic combination, azithromycin–chloroquine, is being developed for intermittent preventive treatment of pregnant women and not specifically to address artemisinin resistance. Apart from endoperoxides and antibiotics, there are only two other candidates in the pipeline, and the earliest any of them could be available is 2016. The most promising candidate in this group is NITD 609. If its safety and tolerability are acceptable, it would be the first non-artemisinin non-peroxide to be studied for proof-of-concept (http://www.mmv.org).

NEW TRANSMISSION-BLOCKING FORMULATIONS

At present, primaquine is the only transmission-blocking drug available, and tafenoquine is the only other candidate in the pipeline. Primaquine causes variable haemolysis in glucose 6-phosphate dehydrogenase-deficient people and is therefore not recommended for those with severe deficiency of this enzyme. Most patients are, however, not aware of their deficiency status. Thus, although WHO recommends the use of primaquine against *P. falciparum* malaria, particularly in low-transmission settings and in the context of

FIGURE 7. Current research and development pipeline of antimalarial medicines



Earliest possible time to launch	> 2016	2016	2015	2013	2011
Likelihood of launching	14%	27%	38%	72%	> 90%

TDR, Special Programme for Research and Training in Tropical Diseases, WHO.
Source: portfolio, for time to and likelihood of launch, Medicines for Malaria Ventures as of November 2010.

pre-elimination or elimination programmes, more widespread use to prevent transmission is limited. In addition, primaquine is contraindicated for pregnant women and infants in the first months of life (WHO, 2010a). As tafenoquine is in the same chemical class as primaquine, similar limitations would apply if it were eventually licensed and recommended for use.

Research on transmission-blocking drugs should focus on identifying drugs that are in a different class from primaquine and tafenoquine. As new drugs are unlikely to be available in the near future, research should also address ways of making primaquine more usable. The most accurate methods for testing for glucose 6-phosphate dehydrogenase deficiency, i.e. the nicotinamide adenine dinucleotide phosphate fluorescence spot test, cytochemical assays and deoxyribonucleic acid sequence analysis, have limited applicability for mass field screening. A highly sensitive, field-ready, low-cost RDT for glucose 6-phosphate dehydrogenase deficiency is needed to allow safe use of primaquine and, if it were to become available, tafenoquine. Modified enzyme assays on dried bloodspots on filter paper are promising for screening in the field.[19] Research is also needed to determine a potentially more appropriate dosing regimen and to establish the prevalence of glucose 6-phosphate dehydrogenase deficiency in people in different regions.

MORE EFFECTIVE VECTOR CONTROL METHODS

Vector control research and development should continue to focus on tools for controlling different vectors, including daytime and outdoor biters, and new insecticides and pesticides, in anticipation of the development of insecticide resistance. Research to support the development of new vector control methods should include entomological research for methods suitable for migrant populations and to control transmission outside the home. Research is also needed on improved personal protection (e.g. treated clothing, tropical repellents). Research on new insecticides and pesticides should include new approaches to minimize the risk of resistance and new categories of pesticides that are effective and not toxic to humans.

NEW DIAGNOSTIC TOOLS FOR MASS SCREENING

Mass screening to detect parasitaemia in both symptomatic and asymptomatic people could be important in the containment of artemisinin resistance. Mass screening requires a highly sensitive, high-throughput, rapid, field-ready, minimally invasive diagnostic test. The tests currently available do not meet these requirements. RDTs are field-ready and fast, but they are not sensitive enough to pick up low levels of parasitaemia and often miss asymptomatic carriers. Polymerase chain reaction (PCR) is highly sensitive, and its sensitivity increases as the blood volume increases, but this type of testing must be performed in suitably equipped laboratories. PCR results are usually not available immediately and the logistics of managing test results can be difficult. Microscopy is generally less sensitive than PCR, and it is often not feasible to conduct mass slide readings in the field (WHO, 2010a).

Several promising diagnostic solutions are being developed, including PCR, loop-mediated isothermal amplification, nucleic acid sequence base amplification and more sensitive RDTs. To permit mass screening, researchers should continue to bring these diagnostics to the market and investigate alternative techniques.

[19] According to interviews conducted by The Boston Consulting Group between May and July 2010.

7.3 Applied and field research

Applied and field research is needed to determine whether the existing interventions can be used in new ways to contain or prevent artemisinin resistance. As a short-term priority, the efficacy of epidemiological or transmission-reduction tools for addressing artemisinin resistance should be evaluated, with a focus on mass screening and treatment, focused screening and treatment, active case detection and mass drug administration. Other applied research priorities are likely to emerge; for example, the use of surveillance to reduce transmission requires additional applied research. More research is also needed to determine whether multiple first-line therapies could be effective in delaying resistance. In this approach, a country's drug policy allows the presence of several different antimalarial therapies in both the public and the private sector, and patients and providers choose the therapy they wish to use. Mathematical modelling suggests that the availability of multiple first-line therapies might delay the emergence of resistant strains more effectively than single-line or rotated therapies (Boni, Smith & Laxminarayan, 2008), but field experience is required to validate this hypothesis. The approach might be difficult to introduce in some countries, because additional training would be required and the logistics and supply chain would be more complex. Before this policy can be recommended, cost-effectiveness studies would also be needed.

EPIDEMIOLOGICAL AND TRANSMISSION-REDUCTION TOOLS

Mass screening and treatment, focused screening and treatment and mass drug administration are being considered for use in pre-elimination and elimination programmes for micro-epidemiological analysis and transmission reduction. As discussed previously, they might also be useful for containing artemisinin resistance. Use of these methods is controversial and requires careful consideration. Each method is designed to reduce the parasite volume dramatically and thereby reduce the potential pool of resistant parasites.

In mass screening and treatment, all persons within a broad geographical area are screened, regardless of whether they have symptoms of malaria. Those for whom a test is positive are given complete malaria treatment. This is a thorough approach, but it can be resource-intensive and logistically challenging. The approach of focused screening and treatment is being applied in high-transmission villages in some areas of western Cambodia within the ARCE programme. Like mass screening and treatment, this approach involves screening all persons within a defined geographical area, but the area is smaller, so that it is less resource-intensive and more feasible logistically. As focused screening and treatment is a more targeted approach and is not delivered synchronously, however, it is unlikely to result in elimination of all resistant parasites and is instead more of an epidemiological tool. Both mass and focused screening and treatment usually rely on PCR for screening, so there is a potential lag of 3 days or more between screening and treatment, making it difficult to follow and treat patients with positive results, especially for migratory, transient or undocumented populations.

The objective of mass drug administration is to eliminate *P. falciparum* parasites from an entire population[20] by treatment of all persons within a geographical area. This approach is easier than mass or focused screening and treatment because no screening is involved, and so patients with a positive result do not have to be re-identified between screening and treatment. Numerous risks are, however, associated with mass drug administration. It can be expensive, depending on the drug(s) used. As treatment is provided indiscriminately, the incidence of adverse side-effects may increase; this is a special problem for people in the early stages of pregnancy or who have other contra-indications. Indiscriminant use of ACTs may also increase the opportunities for the emergence of resistance to artemisinins. As mass drug administration

[20] Active case detection is another tool in pre-elimination or elimination phases, designed to reduce parasitaemia and transmission dramatically. This is discussed in section 7.4, as it is recommended for use in pre-elimination and elimination.

does not involve screening, no information is gathered on the prevalence of infection, and national malaria control programmes and their partners cannot target follow-up interventions to areas with the greatest remaining malaria burden.

In September 2010, WHO Global Malaria Programme convened a group of experts to evaluate the available evidence for use of mass drug administration on the Cambodia–Thailand border. The experts supported the concept of mass drug administration as a potential element of an integrated strategy to contain and eliminate artemisinin resistance, but they identified a number of operational issues that should be addressed before this approach can be pursued broadly. The group therefore recommended that a pilot study of this approach in western Cambodia and eastern Thailand be conducted in late 2011. Lessons from the pilot study will form the basis of a decision on whether to recommend the use of mass drug administration more broadly in tier I containment areas.

Limited evidence is currently available on the effectiveness or long-term effect of mass and focused screening and treatment and mass drug administration in reducing parasitaemia and transmission. For example, the long-term benefits of mass drug administration are heavily debated, some experts suggesting that it probably has no long-term effect on the malaria burden, while others consider that artemisinin-resistant parasites would be eliminated even if malaria is eliminated only temporarily: if malaria returns, the resistant parasites may not.[21] More evidence on the long-term effects of transmission-reduction tools would aid policy-making and guide decision-makers in determining which approach is advisable. Applied and field research is needed to:

- evaluate the relative efficacy of each method in reducing parasitaemia and transmission in both the short and the long term in pilot studies carefully designed for learning and potential up-scaling;
- understand how baseline transmission intensity, population density, health service capacity and other factors influence effectiveness;
- determine which method is most effective in reducing the pool of resistant parasites in both the short and the long term; and
- understand the longer-term implications of these interventions on the emergence and spread of resistant parasites.

When conducting such studies, researchers should also consider which drugs should be used and where, the potential adverse effects or drug–drug interactions, how to mitigate risks to pregnant women and their foetuses and how to treat people with conditions such as glucose 6-phosphate dehydrogenase deficiency.

7.4 Operational research

Various tools and programmes are already being used to contain and prevent artemisinin resistance. Operations research should focus on improving the effectiveness of these tools and programmes and on developing scalable approaches, so that the most successful tools can be used in larger populations and new locations.

SCALABLE MODELS FOR REACHING MOBILE AND MIGRANT POPULATIONS

The highest priority in operational research is to design scalable models for reaching mobile and migrant populations with malaria interventions. The movement and migration of populations infected with

[21] According to interviews conducted by The Boston Consulting Group between May and July 2010.

artemisinin-resistant parasites may drive the spread of resistant parasites from existing foci to other areas. This is a particular concern in the Greater Mekong subregion, where large mobile and migrant populations frequently move within countries and across borders. Limited operational research has been conducted to determine how to reach these populations, and there is no guidance for programme development.

Operational research should be conducted to design and test programmes to address the many questions associated with reaching mobile and migrant populations. For example, what models are most effective for providing interventions for these populations? How can mobile and migrant populations be enumerated and their social networks mapped to allow effective targeting? How can the private retail sector improve access to hard-to-reach populations? Could the programmes be scaled up and at what cost? To what extent can best practices in one setting be applied to another? What types of cross-border collaboration are needed for increased coverage and a decreased malaria burden? Researchers should also study ways to increase effectiveness, such as the 'village malaria worker' approach used in Cambodia. Identification of the best methods for monitoring, training, supervising, retaining and motivating community-based providers would help national malaria control programmes to reach mobile and migrant populations.

BEHAVIOURAL AND SOCIAL RESEARCH

Behavioural and social research should study the behaviour patterns that make some groups more vulnerable to poor health outcomes. Such research might explain why use of oral artemisinin-based monotherapies persists and how best to intervene to increase demand for ACTs and compliance with dosing regimens. The findings of such research could be used to improve the design of information, education, communication and behavioural change interventions to address these challenges.

OTHER PRIORITIES

Operational research should also address other aspects of the containment and prevention of artemisinin resistance, such as tracking suspected treatment failures. A significant increase in the number of suspected ACT treatment failures can indicate the presence of resistance to artemisinins or to the partner drug. This information is infrequently tracked and rarely reported. Health care facilities must record suspected treatment failures continuously and have a system for reporting their findings to the national malaria control programme, for use by policy-makers. This can be difficult in many endemic areas, as patients may not return to a health facility at which they received ineffective treatment, and, even if a patient does return to the same facility, it can be difficult to distinguish the old infection from a new one.[22] Operational research can indicate the best approach for identifying and reporting suspected treatment failures.

Another area in which operational research could be helpful is active case detection. Active case detection involves deliberate follow-up of positive cases to find new cases. Thus, after a patient is found to have malaria, a team screens everyone within a specified range, for example 2 kilometers, of the patient's residence, and all positive cases are then treated. This type of follow-up can be difficult to do in remote areas and for mobile and migrant populations, but it can be useful to identify foci of transmission. Active case detection is recommended and used today in many pre-elimination and elimination settings. Researchers should evaluate which approaches have been most effective and compile best practices for replication elsewhere.

[22] According to interviews conducted by The Boston Consulting Group between May and July 2010.

7.5 Mathematical modelling

As little is known about the mechanism of artemisinin resistance, it is difficult to predict how and when it will spread and to identify which strategies and interventions will be most effective for containing or preventing it. There is also no clear understanding of the impact of artemisinin resistance on malaria-related morbidity and mortality. In such a situation, modelling can guide planning of artemisinin resistance containment, although the results must be interpreted carefully in view of the uncertainties. Several models have been created to guide malaria policy and programmes (Maude et al., 2009; Chitnis et al., 2010).

New models could be designed to estimate the speed and extent of the spread of artemisinin resistance under different conditions, including different transmission intensities; to compare the efficacy, duration and cost of elimination and containment strategies, especially when field studies are not possible; to evaluate the efficacy and predict the effectiveness of various interventions in reducing parasitaemia and transmission; and to identify regional differences that would influence the choice of containment or prevention interventions. Models to estimate the numbers of lives saved should be broadened to include treatment as a variable. These models could then be used to understand how a decrease in the efficacy of ACTs might affect the number of malaria-related deaths.

While models can be helpful, they have limitations. Results obtained with mathematical models should be interpreted in the context of other evidence and broader policy considerations. Field experience should be fed back regularly into the models, so that they can be refined to give more accurate predictions. Although modelling is a lower priority in research on artemisinin resistance, work on artemisinin resistance-related models should continue. Once the mechanisms of resistance are understood, modelling may become more important.

8. Motivate action and mobilize resources

Successful implementation of the GPARC depends on motivating many stakeholders at global, regional and national levels to support or conduct the recommended artemisinin resistance-related activities. Additional funding specifically for artemisinin resistance will be required. Motivating individuals, organizations and governments to support artemisinin resistance containment and prevention will require a concerted effort by leaders in the malaria community.

8.1 Stakeholder motivation

Malaria control and elimination initiatives have accelerated in recent years mainly because of the support from a robust malaria community. Due to the close links between artemisinin resistance management and malaria control and the scope of the effort required, successful implementation of the GPARC depends on motivating the malaria community to support or conduct the recommended activities. The complexity of the response to artemisinin resistance will also require a collaborative, multisectoral approach, with actors from health and other sectors, including education, defense, customs and economic development.

As the coordinator of GPARC implementation, WHO Global Malaria Programme will advocate for support of the GPARC. When requested, WHO Global Malaria Programme can help stakeholders to identify and set priorities for providing support. Coordinated implementation of the GPARC will be the shared responsibility of malaria-endemic countries, WHO Global Malaria Programme and other RBM partners, including: other multilateral organizations, funding agencies, bilateral donors and nongovernmental organizations. For advocacy and implementation of the GPARC, stakeholders can be categorized into the various constituencies described below, with different interests, expertise and modes of operation. Specific priorities for each of the constituencies described below are summarized in chapter 9.

Malaria-endemic countries: in particular, national malaria control programmes and ministries of health. To be effective, they should adopt a multisectoral approach involving all relevant government agencies and departments. Relevant groups will differ by country but could include ministries of finance, economic development, trade and commerce, customs and import and export, transport and migration; and the police and army. For example, military and security forces should facilitate control in sensitive borders areas; likewise, ministries of finance should support government funding for the GPARC;

Multilateral organizations: international organizations formed from collaboration among three or more countries to address global economic and humanitarian issues;

Funding agencies and bilateral donors: include governments or governmental agencies, private or family foundations and other donors, including for-profit companies and private individuals;

Research and academia: organizations conducting laboratory, operational and drug-related research and development, including universities and research centres, product development partnerships and public–private partnerships, research and development units of pharmaceutical companies and other research-based organizations;

Nongovernmental organizations: usually not-for-profit, including both large multinational organizations and community-based organizations;

Manufacturers and distributors of malaria drugs and equipment: pharmaceutical and manufacturing companies producing, marketing and distributing antimalarial drugs, diagnostics and vector control equipment, including insecticide-treated nets.

The development and launch of the GPARC highlights the importance of artemisinin resistance containment and prevention on the agenda of each of these groups. Significant, continuous effort will be required, however, to secure political commitment at the highest levels in governments and organizations, to facilitate cross-sectoral collaboration and to make high-level commitment to artemisinin resistance containment and prevention a day-to-day activity of each group. Efforts by WHO Global Malaria Programme and the wider RBM partnership to motivate stakeholders will be supported by:

- a central repository for GPARC-related information;
- a compelling set of messages customized for each group;
- regular communication and dissemination of information on progress and needs;
- identification of opportunities for introducing updates and messages on the GPARC into large meetings organized by stakeholders;
- a clear plan of engagement with endemic countries, especially those in which resistance is suspected or which are close to areas with artemisinin resistance; and
- a network of high-profile officials to spread messages formally and informally.

8.2 Resource mobilization

ESTIMATED FUNDING REQUIREMENTS FOR CONTAINING ARTEMISININ RESISTANCE

Containment of artemisinin resistance in the Greater Mekong subregion and prevention of its emergence or spread to other regions is a priority for funding in the short term. Given the significant overlap between malaria control and artemisinin resistance containment, a fully funded and implemented malaria control agenda would address many of the needs to manage artemisinin resistance. Maintaining and, where possible, increasing funding for malaria overall should be a priority in implementation of the GPARC.

Additional resources will be required specifically for artemisinin resistance containment and prevention. The estimated funding requirements, by activity, are described below and shown in Table 5. As experience in artemisinin resistance containment and prevention is limited, further analysis will be needed in order to verify these estimates and to estimate the cost of implementation of programmes in each context.

Tier I and II areas: The most important funding priority for artemisinin resistance containment and prevention is programme implementation in tier I and II areas. In the ARCE programme in Thailand and Cambodia, containment and prevention programmes cost US$ 10–20 in tier I and US$ 8–10 in tier II areas annually per person at risk. The exact cost of other containment programmes will vary by area, depending on the intensity of effort required and the existing capacity and infrastructure.

Tier III areas: In tier III areas, the focus is on malaria control. Modest additional costs are anticipated for increased monitoring of drug efficacy (when it is not done already) and enforcement of bans on monotherapies and substandard and counterfeit drugs. These additional costs are estimated to be US$ 50 000 –100 000 per country per year for monitoring[23] and roughly US$ 500 000 per country per drug quality enforcement programme, depending on the sophistication of the national drug regulatory authority.

[23] WHO Global Malaria Programme estimate.

Global and regional coordination: Global and regional coordination is estimated to cost US$ 8–14 million per year, with US$ 3–4 million per year for global and regional coordination of the response plan and an additional US$ 5–10 million for coordination of monitoring and surveillance.

Research: On the basis of estimates by the Medicines for Malaria Venture, the cost of accelerating research and development for non-artemisinin antimalarial medicines will be US$ 240–250 million over 5 years, or about US$ 50 million per year. The funding requirements for artemisinin resistance-specific laboratory research, beyond what is funded today, are estimated to be US$ 10–15 million annually.[24] Incremental investment to support applied or operational research is incorporated in the person-at-risk cost estimates for tiers I and II and is therefore not included as a separate research cost.

TABLE 5. Estimated annual funding requirements for containing artemisinin resistance by tier

COST CATEGORY	ACTIVITIES	ESTIMATED ANNUAL COST (US$)
Tier I	• Treatment (including ACTs, transmission-blocking drugs and management of monotherapies, counterfeits and substandard drugs) • Drug efficacy monitoring and surveillance • Diagnosis (RDTs and microscopy) • Prevention: vector control • Artemisinin resistance-specific education and training • Strategies for mobile and migrant populations	~ 10–20 per person at risk (depending on level of infrastructure)
Tier II	• All tier I costs, except focused screening and treatment and confirmatory studies	~ 8–10 per person at risk
Tier III	• Monitoring of ACT efficacy* • Additional costs to enforce bans on monotherapies and counterfeit and substandard drugs	~ 50 000–100 000** ~ 500 000***
Global	• Overall • Coordination of the GPARC • Monitoring and surveillance	~ 8–14 million ~ 3–4 million ~ 5–10 million
Research	• Overall • Additional non-artemisinin drug development costs • Acceleration of laboratory research (including molecular markers)	~ 60–65 million ~ 50 million ~ 10–15 million

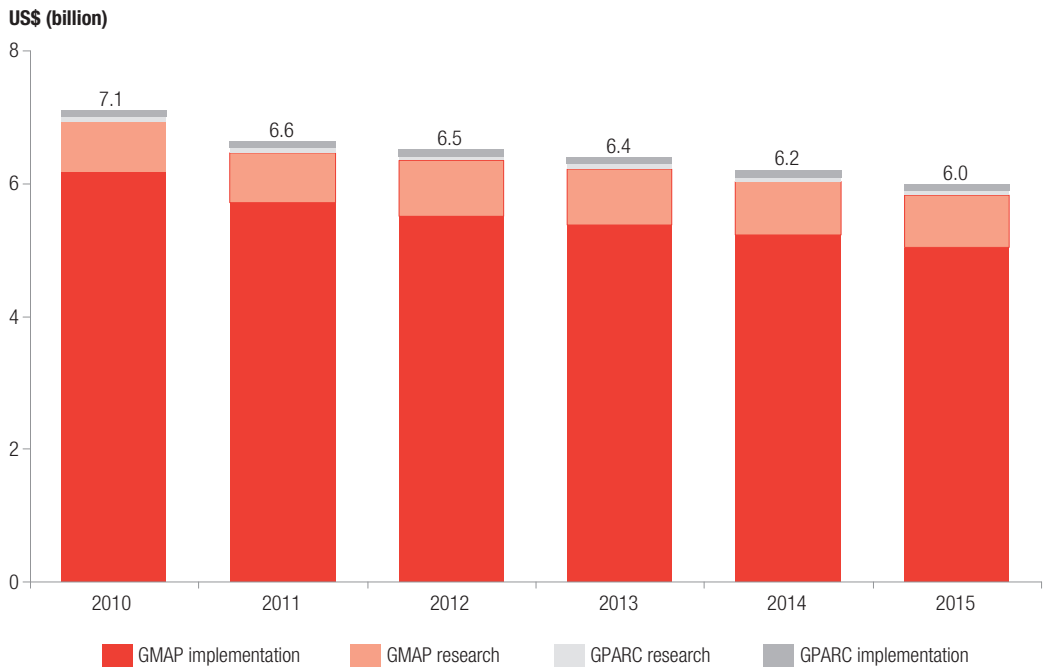
* Applies only to tier III countries that are not yet monitoring the therapeutic efficacy of ACTs in compliance with the WHO protocol; ** Assumes per country US$ 50 000–100 000 for three studies per year or six studies in a given 24-month period (source WHO Global Malaria Programme); *** Cost varies significantly by country, from approximately US$ 260 000 per year for an advanced national drug regulatory authority to over US$ 700 000 per year for the least developed national drug regulatory authorities (source: United States Pharmacopeia Promoting the Quality of Medicines programme).

In total, full funding of artemisinin resistance containment and prevention would be upwards of US$ 175 million per year globally, with just over US$ 100 million for programme support and about US$ 65 million for research and development. These estimates are based on the assumption that tier I and II areas are limited to those in and around the currently suspected foci in Cambodia, Myanmar, Thailand and Viet Nam.

When the funding requirements for managing artemisinin resistance are added to the estimates for malaria control and elimination described in the *Global Malaria Action Plan* (US$ 6.9 billion in 2010, including US$ 6.2 billion for control and elimination and US$ 0.7 billion for research), the total cost of controlling malaria and containing artemisinin resistance is estimated to be US$ 6–7 billion annually through 2015 (Figure 8).

[24] Estimate based on current funding for laboratory research.

FIGURE 8. Estimated funding required for both malaria control and artemisinin resistance containment



Global Malaria Action Plan (GMAP) implementation costs include diagnosis and treatment (ACTs, RDTs and severe case management), monitoring and evaluation, malaria programme (including community health workers, training, infrastructure and institutional strengthening) and prevention.

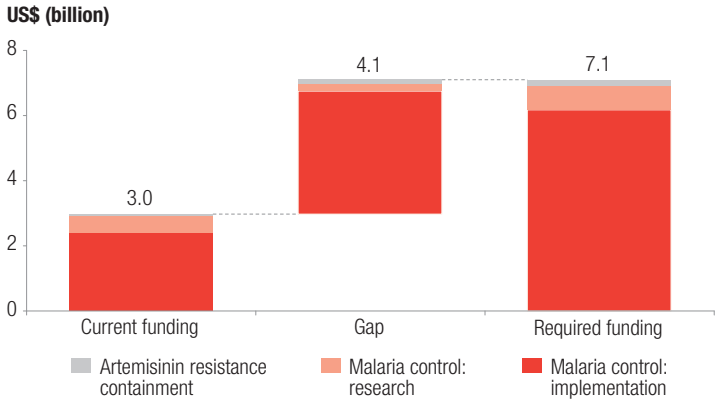
FUNDING GAPS FOR MALARIA CONTROL AND ARTEMISININ RESISTANCE CONTAINMENT

Much of the recent success in malaria control can be attributed to a dramatic increase in funding. In 2009, total funding for malaria was estimated to be nearly US$ 3 billion, including:

- nearly US$ 1.6 billion disbursed by the GFATM, the President's Malaria Initiative, the World Bank and Organization for Economic Co-operation and Development countries for malaria control programmes, as stated in the 2010 RBM *Malaria Funding and Resource Utilization* report (Johansson, Cibulskis & Steketee, 2010);
- an estimated US$ 923 million spent by endemic countries, households and other sources (RBM, 2008; WHO, 2008);
- US$ 542 million for malaria research and development contributed by the United States National Institutes of Health, the Bill & Melinda Gates Foundation and other research and development donors; and
- approximately US$ 40 million to manage artemisinin resistance (Johansson, Cibulskis & Steketee, 2010).

Despite the increase in funding, more than US$ 4 billion is still needed to fully control malaria and contain artemisinin resistance, based on the cost estimates in the *Global Malaria Action Plan* (Figure 9).

FIGURE 9. Gap in funding for malaria control and artemisinin resistance containment and prevention



Sources for existing malaria funding for implementation: GFATM (actual disbursements through round 8), the President's Malaria Initiative (actual disbursements), the World Bank (disbursements assumed to be equal to those in 2008, from project appraisal documents or, if not available, by assuming a constant flow of funds throughout the life of a project), the United States Agency for International Development (from malaria budget: http://www.usaid.gov/policy/budget/cbj2007/si/malaria.html), national spending and other international donors (from *World malaria report 2008*, Annex 7) and private household spending (from *Global Malaria Action Plan*, appendix on funding estimates). Sources of existing funding for research and development: United States Agency for International Development (http://www.usaid.gov/our_work/global_health/ home/Funding/funding_rd.html), Bill & Melinda Gates Foundation and pharmaceutical companies (G-Finder reports 2008 and 2009, assuming that research and development spending was constant in 2009 and will continue at that level), National Institutes of Health and other research and development sources (historical) through 2006 from malaria strategy work, above; for 2007 onwards, from G-Finder assuming that it is constant since 2008). The Boston Consulting Group analysis.

Insufficient funding for malaria control and artemisinin resistance containment could have severe consequences in tier I and II areas, including more rapid spread of resistance. Inadequate funding in tier III areas would mean that those areas would not be sufficiently protected if artemisinin resistance emerged or spread, nor are they likely to have resources in place to identify decreased drug efficacy promptly. Funding artemisinin resistance containment in the Greater Mekong subregion today is an investment to prevent artemisinin resistance from reaching high-transmission areas, including much of Africa. If artemisinin resistance were to emerge in another region, the cost of managing it would increase dramatically, particularly if the affected region had higher transmission. Closing the malaria funding gap, even incrementally, will not only improve malaria outcomes overall but will increase the likelihood that artemisinin resistance can be contained effectively.

INCREASING AND SUSTAINING FUNDING

Like all aspects of the GPARC, increasing and sustaining sufficient funding for malaria control and artemisinin resistance containment will require commitment from stakeholders at global, regional and country levels. At the global level, multilateral organizations, funding agencies and bilateral donors should increase and accelerate funding for malaria control in all endemic countries. In addition, they should fund activities for artemisinin resistance containment and prevention, especially in tier I and II areas. Coordination is important in order to match funders to relevant projects and ensure that resources are allocated as effectively as possible. Tracking funding and implementation globally and within programmes and grants should be a priority for funders as a means of following progress, increasing the effectiveness of their funding and guiding future investments. Table 6 gives additional details of priorities for global engagement.

TABLE 6. Global priorities in funding malaria activities

AREA	STAKEHOLDER	ACTIVITIES
Increase funding	Funding agencies, bilateral donors and endemic countries	Increase and accelerate funding for malaria control for all tier areas. Fund specific projects and programmes for containing and preventing artemisinin resistance, especially in tier I and tier II areas.
Coordinate funding	WHO, Bill & Melinda Gates Foundation, GFATM, United States Agency for International Development and President's Malaria Initiative, others funders	Predict the resources needed for global and country activities, and update as required. Identify existing donors for malaria control and new donors interested in funding containment of artemisinin resistance; prepare specific approaches for each donor. Help to match donors to projects or areas. Work with endemic countries in planning resource use, including increasing domestic funding for malaria control.
Track progress in use of funds	WHO, Bill & Melinda Gates Foundation, others funders (with individual monitoring of each grant)	Track use of funds, monitor progress and provide accountability. Coordinate regional and country activities, and share best practices. Make a contingency plan, with coordination of emergency funds, in case of rapid spread of artemisinin resistance.

At country level, the ministries of health and finance should work together to ensure adequate funding for malaria control in general and artemisinin resistance containment or prevention specifically. Before they identify and allocate funds, the ministries should first evaluate the requirements for implementation of the GPARC in their country. The resource requirements will vary significantly among countries and even areas within a given country, depending on the tier classification. In subsequent resource planning, new funding for artemisinin resistance containment and prevention should be sought when possible. All potential funding sources should be explored, including domestic organizations, international sources like the GFATM and other funding agencies or bilateral agreements. Nongovernmental and community-based organizations should continue to advocate for funding to secure grants for specific containment-related projects, in order to supplement resources mobilized by the government.

The rapid increase in resources for malaria in the past decade may be entering a much slower growth period due, in large part, to the global financial crisis. Significant progress towards closing the malaria funding gap may be difficult. Fortunately, even partial funding can be valuable, especially if it is used for the highest priority activities. In view of the resource constraints, the first priority for funding agencies should be containment programmes in areas for which there is evidence of artemisinin resistance. A second priority should be monitoring and surveillance of drug efficacy in endemic countries, especially in those in which studies have not been conducted in recent years. In order to maximize the impact of available resources, funding agencies and other stakeholders should harmonize their investments.

9. Stakeholders' priorities

The GPARC was developed with input from all of the constituencies of the RBM Partnership and is designed to serve as a rallying cry for all members of these groups. Given the complexity of the required response to artemisinin resistance, stakeholders outside the traditional malaria or public health communities will also need to be engaged. In this section, the priorities for each stakeholder or constituency in supporting successful implementation of the GPARC are summarized.

As most of the current malaria control and elimination activities, outlined in the *Global Malaria Action Plan*, will also benefit the containment and prevention of artemisinin resistance, stakeholders are encouraged to continue, expand or accelerate the activities they currently conduct or support. The purpose of this section is to help stakeholders identify additional areas in which they can contribute specifically to the urgent issue of artemisinin resistance containment and prevention. Items of high priority for action are highlighted for each constituency. The expectation is that each stakeholder will use these recommendations as a basis for designing a specific programme for containment or prevention of artemisinin resistance that is consistent with its mandate.

It is anticipated that stakeholders will work closely together, each focusing on activities within its functional area of expertise, to address cross-cutting issues in artemisinin resistance. For example, ensuring timely monitoring of therapeutic efficacy will involve resource mobilization, technical guidance from WHO Global Malaria Programme and other partners, studies in the field, the reporting of results and, potentially, changes in national policies. In order to determine the priority actions, each stakeholder's ability to contribute in eight functional areas was analyzed: global policy and norms, surveillance and reporting, containment and implementation, resource mobilization, advocacy and political engagement, research, local policy and regulation, and emergency response.

Table 7 summarizes the areas in which each constituency can act. As malaria-endemic countries will implement the GPARC, they are involved in all functions. In view of WHO's mandate to represent and support countries, the areas of involvement of WHO Global Malaria Programme largely mirror those of the countries, with a focus on policy guidance, global surveillance and technical expertise. WHO Global Malaria Programme will continue to monitor and coordinate implementation of the GPARC and, to do so, has created a new unit dedicated to antimalarial drug resistance, the Drug Resistance and Containment unit. WHO Global Malaria Programme will also rely on WHO regional and country offices in coordinating assessment of the level of threat of artemisinin resistance in a given area, prepare a detailed, feasible response, build capacity for monitoring and mobilize the necessary stakeholders and resources.

Successful implementation of the GPARC depends on the support and cooperation of many other groups. For example, research and academic institutions should conduct research on artemisinin resistance and support monitoring and surveillance in collaboration with national malaria control programmes; they may play a secondary role in resource mobilization and advocacy. The main role of funding agencies, including the GFATM and bilateral donors, is resource mobilization, advocacy and political engagement, and their funding should support activities in all functions. Nongovernmental organizations should support the implementation of containment and prevention programmes and will also support resource mobilization and advocacy. The private sector has a variety of roles to play, including supporting containment programmes, advocacy and research. The specific priorities by constituency are listed below.

TABLE 7. Primary and secondary areas of involvement by stakeholder segment

	Global policy and norms	Surveillance and reporting	Containment and implementation	Resource mobilization	Advocacy and political engagement	Research	Local policy and regulation	Emergency response
Endemic countries (tier I, II and III)	✓	✓	✓	✓	✓	✓	✓	✓
Multilateral organizations WHO Global Malaria Programme	✓	✓	✓	✓	✓	✓*	✓	✓
Multilateral organizations WHO regional and country offices	✓	✓	✓	✓	✓		✓	✓
Multilateral organizations all other			✓	✓	✓			✓
Research and academia		✓		✓	✓	✓		
Nongovernmental organizations			✓	✓	✓			✓
Private sector		✓	✓	✓	✓	✓		✓
Funding agencies and bilateral donors		✓	✓	✓	✓	✓	✓	✓

✓ Primary ✓ Secondary

* Research part conducted by Special Programme for Research and Training in Tropical Diseases, WHO.

MALARIA-ENDEMIC COUNTRIES

- Conduct routine studies of therapeutic efficacy to identify or monitor artemisinin resistance and classify areas of the country by risk level.
- Prepare a context-specific containment or prevention plan, consistent with the recommendations of the GPARC.
- Secure funding for malaria control and artemisinin resistance containment or prevention; make sure that grant applications or operational plans for international funding include containment or prevention activities, and secure domestic funding where possible.
- Design and enforce policies and regulations on the manufacture, distribution (import and export) and use of oral artemisinin-based monotherapies and substandard and counterfeit treatments.
- Participate actively in subregional monitoring networks and in cross-border collaboration to ensure that malaria interventions reach populations in border areas.

WHO GLOBAL MALARIA PROGRAMME

- Provide leadership, oversight and coordination of the GPARC, including increasing awareness about the urgency of the threat of artemisinin resistance, supporting resource mobilization and communicating regularly with implementing partners.
- Prepare, communicate and promote adoption of norms, standards and policy guidelines on artemisinin resistance, with advice from the technical expert group.

- Regularly assess progress in implementing the GPARC, including continuous monitoring of global drug resistance, in collaboration with endemic countries and funders and with guidance by the technical expert group. Make results available publicly.
- Provide technical guidance and support for local containment and prevention projects.
- Identify the main threats and opportunities related to artemisinin resistance, and be prepared to initiate and coordinate an emergency response if needed.

The Drug Resistance and Containment unit and WHO Global Malaria Programme receive guidance and oversight from an external technical expert group on antimalarial drug resistance in order to ensure accountability.

WHO REGIONAL AND COUNTRY OFFICES

- Help countries to assess the level of threat of artemisinin resistance in a given area and to prepare detailed, feasible response plans.
- Build capacity for monitoring, including coordination with regional and subregional organizations and academic institutions.
- Mobilize the necessary stakeholders and resources to support artemisinin resistance prevention and containment plans.

MULTILATERAL ORGANIZATIONS

- Advocate for the inclusion of artemisinin resistance priorities in global malaria control and research agendas; assist in communication and dissemination of messages.
- Coordinate the international mobilization of resources dedicated to artemisinin resistance-specific activities and consider funding containment or prevention projects directly.
- Provide assistance and coordination on issues with cross-border implications, such as mobile and migrant populations.
- Support malaria-endemic countries and partners in local implementation of artemisinin resistance containment and prevention activities.
- Be prepared to support emergency response plans if artemisinin resistance spreads to high-transmission areas faster than anticipated.

RESEARCH AND ACADEMIA

- Conduct research in the five areas outlined in chapter 7 of the GPARC.
- Support monitoring and surveillance activities coordinated by the national malaria control programme.
- Support resource mobilization or advocacy for research priorities as appropriate, including tracking and reporting on funding for research and development to highlight gaps.

NONGOVERNMENTAL ORGANIZATIONS

- Coordinate with and provide technical assistance to national malaria control programmes and ministries of health to implement integrated programmes for containment and prevention of artemisinin resistance in tier I and II areas, including activities to cover hard-to-reach populations.

- Accelerate efforts to attain universal access to prevention, diagnosis and treatment of all confirmed malaria cases in tier I and II areas, and continue malaria control activities in tier III areas.
- Provide technical assistance and support to national malaria control programmes and ministries of health to conduct therapeutic efficacy studies and surveillance.
- Conduct training and education for prevention, diagnosis and treatment, for health care providers, retailers (informal private sector) and patients.
- Advocate for sustained malaria control and resource mobilization.

PRIVATE SECTOR

Companies that manufacture or market quality-assured ACTs

- Continue to produce, distribute and advocate for quality-assured ACTs, in accordance with current WHO *Guidelines for the treatment of malaria* and the Essential Medicines Lists of endemic countries; provide adapted information and educational materials on the rational use of each ACT to national drug regulatory authorities, national malaria control programmes and other stakeholders.
- Increase efforts to ensure that ACTs reach high-priority areas and to avoid shortages of quality-assured ACTs.
- For antimalarial medicines that exist as fixed-dose combinations, phase out co-blistered or loose associations in favour of fixed-dose combinations as soon as possible.
- Promptly share new data from monitoring and surveillance of artemisinin resistance.

Companies that manufacture or market monotherapies or substandard artemisinin-based drugs

- Halt production and distribution of oral artemisinin-based monotherapies and substandard antimalarial drugs.
- Set up operations that abide by national regulations or WHO guidelines on monotherapies and substandard drugs and adhere to the policy that is most stringent.
- Make the production of fixed-dose combinations a priority.

Companies that manufacture or market diagnostics or vector control tools

- Increase capacity to produce and distribute vector control supplies and high-quality diagnostics in tier I and II areas.
- Provide additional training and support to containment programmes in tier I areas.
- Consider regional marketing approaches to help patients recognize and properly use recommended malaria interventions.

FUNDING AGENCIES AND BILATERAL DONORS

- Fund programmes for containing and preventing artemisinin resistance in tier I and II areas.
- Increase funding for malaria control to accelerate universal coverage (especially in tier I and II areas) and support monitoring and surveillance of drug efficacy in endemic countries.
- Support research priorities and capacity development for research, including the development of non-artemisinin-based drugs, laboratory science and operational research.
- Design mechanisms for rapid mobilization of resources when resistance is identified or an emergency response plan is triggered.
- Act as an advocate on key issues, such as putting pressure on countries with producers of monotherapies and counterfeit antimalarial medicines to enforce WHO medicines.

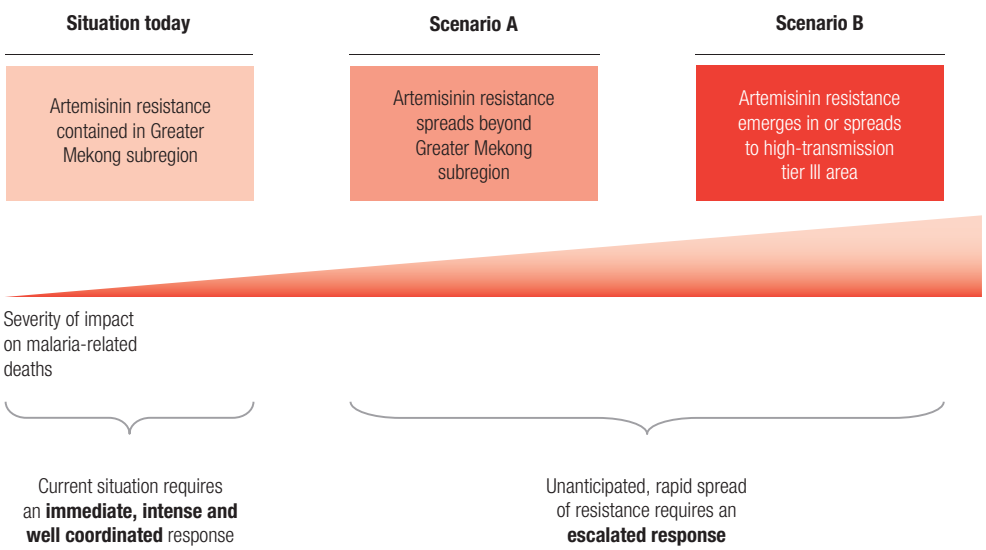
10. Emergency mobilization plan

As described in the introduction, the GPARC is based on current information about where artemisinin resistance exists and on assumptions about the speed of its potential spread. The severity of the situation today necessitates an immediate, intense, well-coordinated response. Should artemisinin resistance spread more rapidly than originally anticipated, an escalated response will be needed. The emergency mobilization plan is not a separate plan but builds on GPARC recommendations for preventing and containing artemisinin resistance. The goal of the emergency mobilization plan is to prevent artemisinin resistance from spreading to a high-transmission area or, if resistance appears in a high-transmission setting, to contain it as quickly as possible.

TWO SCENARIOS THAT TRIGGER AN EMERGENCY RESPONSE

Two potential scenarios in which artemisinin resistance appears to have spread beyond the Greater Mekong subregion should trigger emergency mobilization to varying degrees (Figure 10). In scenario A, artemisinin resistance is no longer contained in a focal geographical area. Its presence outside of the Greater Mekong subregion (e.g. in another country in Asia) would suggest not only an immediate threat to the area in which it appears but also an increasing likelihood that resistance will spread to high-transmission areas. In scenario B, artemisinin resistance has emerged in or spread to a high-transmission area (e.g. in Africa). In either scenario, artemisinin resistance should be confirmed, in accordance with WHO recommendations, before a full-scale emergency response is launched. In view of the urgency of the threat, however, if there is credible evidence for either scenario, containment efforts should be planned and implemented in parallel with confirmatory studies. The technical expert group on antimalarial drug resistance, to be convened by WHO Global Malaria Programme, will define trigger points for each scenario. As needed, the group will evaluate the evidence and determine when those trigger points have been reached and emergency mobilization is required.

FIGURE 10. Two potential scenarios that will trigger emergency mobilization



THREE ELEMENTS OF THE EMERGENCY MOBILIZATION PLAN

If either scenario occurs, three actions should be launched immediately and simultaneously:

- global advocacy to escalate artemisinin resistance to the top of global health and development agendas and motivate the global community to coordinated action;
- intensive, coordinated containment activities in areas with newly confirmed artemisinin resistance (in accordance with tier I recommendations in the GPARC) and rapid scaling-up of precautionary measures in all neighbouring areas (in accordance with tier II recommendations); and
- a significant increase in funding and, if necessary, potential reallocation of funding from existing tier I areas to new tier I areas in order to focus the response on the resistance 'frontier'.

The intensity of the emergency response will depend on the scenario and the severity of the threat of spread of resistance.

Global advocacy

The emergence of artemisinin resistance in the Greater Mekong subregion is of serious concern, but its rapid spread of beyond this subregion would make it an even greater global threat. To reflect the heightened urgency of such a situation, global advocacy would be required to mobilize a large-scale, coordinated containment response and to escalate the issue to the top of global health and development agendas. WHO would initiate advocacy, and other multilateral organizations, donors and other stakeholders could continue and expand it.

Advocacy should focus on the following objectives:

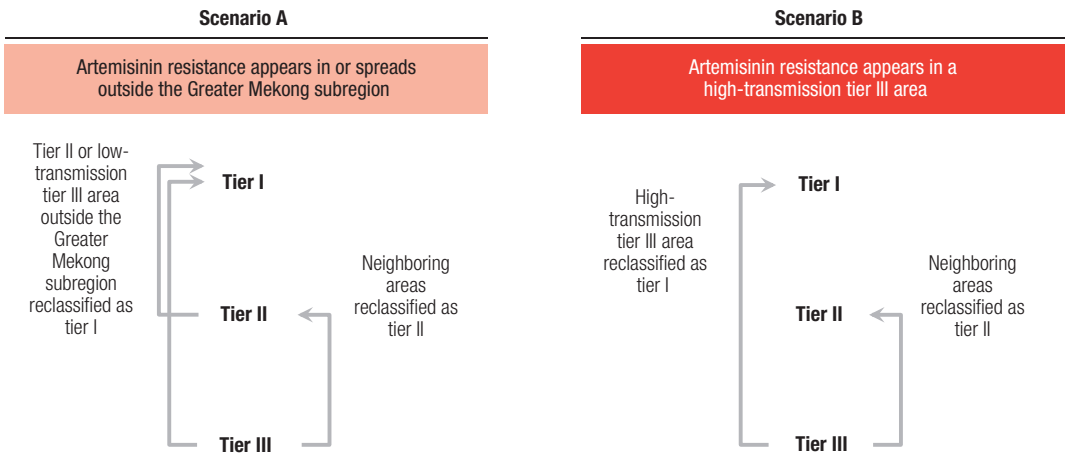
- Ensure that artemisinin resistance containment becomes an immediate, urgent priority.
- Spur immediate action by all relevant stakeholders, especially national malaria control programmes and their partners responsible for on-the-ground containment.
- Mobilize resources for broad containment efforts, including rapid identification of donors and rapid disbursement of funds.

For the response to be successful, the most senior leaders in global health should turn political leaders into advocates to mobilize funds. Advocacy should also include a communication campaign to reach decision-makers, donors and the populations of affected areas.

Intensive, coordinated containment activities

If artemisinin resistance is confirmed outside the Greater Mekong subregion or in a high-transmission setting, the area in which resistance has been confirmed should immediately be reclassified as tier I. The new tier I area will become the 'frontier' of resistance and the highest priority for aggressive containment. All recommended tier I activities, as described in chapter 3, should be implemented immediately (Figure 11).

FIGURE 11. Change in tier classification after confirmation of artemisinin resistance

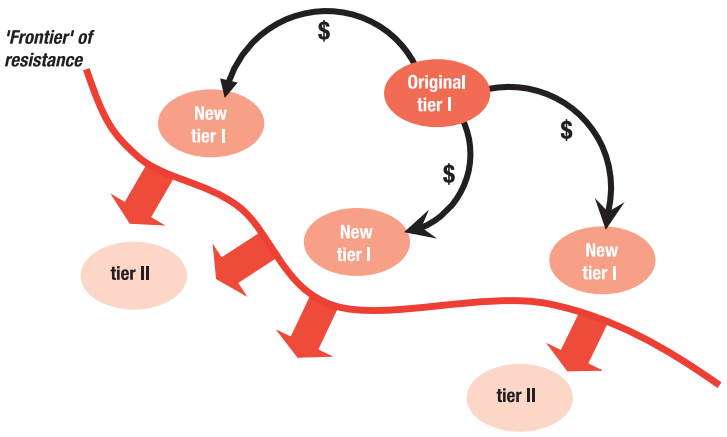


As stated previously, a prompt, multifaceted response will be required to contain and eliminate resistant parasites. The extent of the containment effort will depend mainly on the size of the affected region, including both tier I and tier II areas. In tier I areas, current control activities should be accelerated to reach 100% of the populations at risk as soon as possible, including provision of preventive measures, parasitological diagnosis, quality-assured ACTs and potentially transmission-blocking drugs, as well as activities specifically for the containment and elimination of resistant parasites. At the same time, precautionary measures should be taken in all areas neighbouring newly designated tier I areas. Areas bordering a new tier I area are automatically reclassified as tier II areas, triggering implementation of all recommended tier II activities.

Significant increase in funding or reallocation of existing funds

A significant increase in funding, and perhaps a reallocation of existing funds, will be required to support emergency mobilization when it is triggered. To prepare for this, the malaria community should consider preemptively identifying donors who are willing to commit funding for emergency mobilization. Ideally, sufficient new funds will be mobilized; however, if there is insufficient new funding to address resistance at the 'frontier', existing funds might have to be shifted from original tier I areas to new tier I areas to prevent further spread of resistance (Figure 12).

FIGURE 12. Reallocation of funding to the 'frontier' of resistance



The amount of funding required will depend in large part on the magnitude of the required containment effort, which in turn depends on the number of areas now considered tier I and II, the size of the population at risk in each area and the complexity of implementation in these areas.

STEPS TO ENSURE THAT THE GLOBAL COMMUNITY IS PREPARED

To ensure that the global community is prepared for emergency mobilization, several preliminary steps should be taken.

- The technical expert group on antimalarial drug resistance, to be convened by WHO Global Malaria Programme, should determine the triggers for emergency mobilization, i.e. the extent of spread of artemisinin resistance that warrants an emergency response. The group should also be prepared to review and assess evidence of new foci of artemisinin resistance to determine if and when the trigger point has been reached.
- The roles and responsibilities of each stakeholder in emergency mobilization should be clearly delineated, and each stakeholder should be aware and engaged.
- Potential funding and administrative resources should be identified, and donors should commit funding for emergency mobilization in advance.

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Annex 1. Case study of containment of artemisinin resistance in Cambodia

Given the ongoing initiatives in western Cambodia to manage artemisinin resistance, this country provides a good example of how many of the solutions described in the GPARC might be implemented in the field. Several experiences are described below; additional documentation, especially on the ARCE programme, can be found in the *Global report on antimalarial drug efficacy and drug resistance, 2000–2010* (chapter 4), and a detailed summary of the activities is available on the WHO website at: http://www.who.int/malaria/diagnosis_treatment/arcp/en/index.html.

VECTOR CONTROL

Artemisinin resistance containment in Cambodia, at the border with Thailand, includes widescale distribution of vector control tools in two containment zones.[25] Vector control in these zones includes procurement and distribution of long-lasting insecticide nets and long-lasting insecticide hammock nets and rapid monitoring to assess and monitor bed net distribution and coverage. High coverage has been achieved in both zones: 92% of target villages received nets; a coverage rate of 1.79 people per net was achieved; 96% of the long-lasting insecticide nets delivered were observed in houses during assessment; and 70% of the long-lasting insecticide nets delivered were currently in use, 99.7% of which had been used the previous night. While it is difficult to attribute progress to a single intervention, the high level of vector control appears to have contributed to the initial success of the project in sustaining a low number of malaria cases in zone 1.

PROVIDING SUBSIDIZED ACTS TO THE PRIVATE SECTOR

In 2002, Cambodia was the first country to test and scale-up a programme to provide subsidized ACTs to the private sector (D. Socheat, personal communication). The project was implemented by Population Services International, with financial support from the GFATM. To promote the sale of subsidized products, Population Services International sent teams to local shops to disseminate information materials. They also undertook nationwide information campaigns with various communication modes and trained private sector providers in proper case management.

Monitoring and evaluation of the project indicated encouraging results. Penetration with first-line ACTs increased from 22% of sampled public sector outlets in 2004 to 40% in 2007; in 2008, the penetration rate was 64% (http://www.actwatch.info). The project also met various challenges. First-line ACTs were sold at much higher prices than the recommended retail price printed on the box (US$ 1.07 on average versus US$ 0.5 on the box). Moreover, despite the fact that a large proportion of shops now stocked ACTs, actual sales of first-line ACTs remained low (28% of sales in 2009, versus 22% for other ACTs, 24% for oral artemisinin-based monotherapies and 26% for non-artemisinin-based monotherapies). To address these issues, the Cambodian malaria control programme applied for the first phase of the Affordable Medicines

[25] Zone 1 covers areas in which artemisinin resistance has been detected. In Cambodia, it covers about 270 000 people in four provinces: all of Pailin and parts of Battambang, Pursat and Kampot. Zone 2 covers areas in which there is no evidence of resistance but the risk is high because they are close to zone 1. It includes nine provinces with a total population of more than 4 million (excluding towns).

Facility – malaria to strengthen existing behavioural change communication and training activities and test new ones.

The Affordable Medicines Facility – malaria was launched in Cambodia during the third quarter of 2010, and the first round of ACTs arrived in August. The results of pilot studies both in Cambodia and in eight other areas will be used to decide on future programmes to improve access to ACTs in the private sector.

INTERRUPTING THE IMPORTATION AND SALE OF ORAL ARTEMISININ-BASED MONOTHERAPIES

The Cambodian Minister of Health used a multi-pronged approach with communications, meetings with stakeholders and stringent enforcement to implement a ban on oral artemisinin-based monotherapies. In March 2009, the Cambodian Ministry of Health issued an official letter banning oral artemisinin-based monotherapies in Cambodia. One month later, a meeting of national stakeholders was held to disseminate the announcement to 54 private companies. In July 2009, a provincial meeting was held to inform stakeholders at local level about the new ban and to raise awareness about the problems associated with use of monotherapies. Since then, the Government has conducted numerous follow-up visits and has confiscated illegal drugs when found (Schwartze et al., 2010).

REMOVING SUBSTANDARD AND COUNTERFEIT ANTIMALARIAL DRUGS

In 2003, the joint United States Pharmacopeia and United States Agency for International Development programme, Promoting the Quality of Medicines, was launched in Cambodia to provide technical assistance for post-marketing surveillance to track the quality of medicines. After finding that 16.2% of antimalarial medicines sampled in the private sector were of poor quality, the Cambodian Government took action against substandard and counterfeit drugs. Initially, lack of coordination among various ministries posed a barrier to the success of this effort; therefore, the Government created an interministerial committee in 2005 to prepare an action plan to reduce the volume of substandard and counterfeit medicines significantly. The plan, which focused on strengthening post-marketing surveillance and banning sales from five manufacturers in the country, resulted in a 65% reduction in unlicensed pharmaceutical outlets over 6 months (Moszynski, 2010).

INCREASING ACCESS TO MALARIA SERVICES THROUGH VILLAGE MALARIA WORKERS

In 2002, the Cambodian Government's National Centre for Parasitology, Entomology and Malaria Control, with technical and financial support from WHO and the European Union, launched the 'village malaria volunteers' project on the basis of positive results obtained in a trial of the efficacy of insecticide-treated nets in Ratanakiri Province in 2001 (Sochantha et al., 2006). The programme is a key component of the national strategy to strengthen community-based malaria control (Yasuoka et al., 2010; http://www.fhi.org/en/CountryProfiles/Cambodia/res_village_malaria_workers_Cambodia.htm). Its objectives are to increase access to diagnosis and treatment and improve case detection and management in high-risk, remote areas, which represent about 62% of the country. The Cambodian national malaria control programme has recruited two malaria workers per village and given them 3 days of training in prevention, proper diagnosis, treatment and other elements of malaria case management. Village malaria workers are supervised and supplied with free RDT kits and antimalarial medicines monthly by the national malaria

control programme, which also gives them about US$ 5 per month in compensation. The workers perform RDTs on any villager suspected of having malaria and, for positive cases, provide ACTs according to the national guidelines. They are able to provide services for free when needed and regularly refer severe cases to health posts.

The project has shown that village malaria workers could be an effective means of improving access to early diagnosis and treatment of malaria. The project is also helping to move malaria treatment from the private to the public sector, where only recommended drugs are dispensed. Furthermore, the local availability of quality-assured malaria treatment has significantly reduced the use of counterfeit medicines. Given the success of the programme, village malaria workers should be considered as a potential source of additional services, including active case detection, follow-up or mapping.

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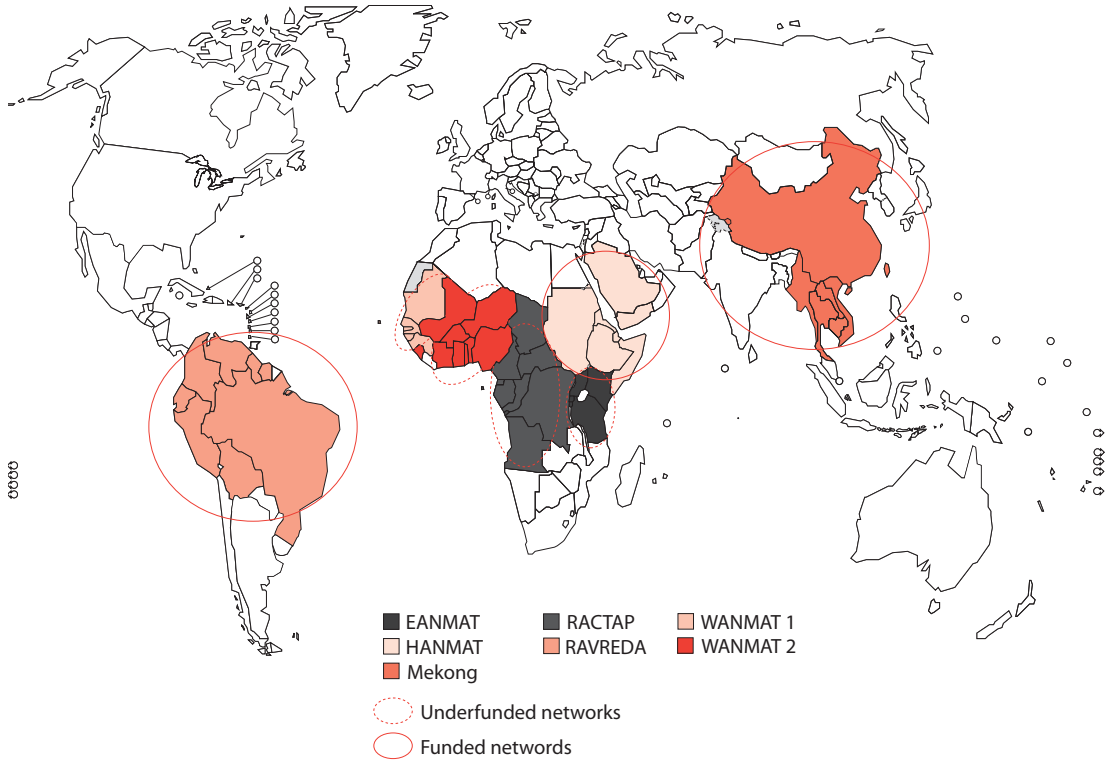
Annex 2. Subregional monitoring of therapeutic efficacy of antimalarial medicines

Many of the subregional monitoring networks that once existed to complement country monitoring are now underfunded or no longer active. Before the introduction of ACTs, seven subregional networks monitored antimalarial efficacy (Figure A2.1). When such networks are sustainably funded and effectively managed, they can have several important benefits, including:

- encouraging and providing incentives for countries to conduct regular monitoring of drug efficacy, including sharing of best practices in conducting therapeutic efficacy studies;
- staff training including protocols, implementation and reporting;
- more effective management of problems in border areas, by sharing data and setting up sentinel sites on both sides of a common border;
- identification of subregional trends in resistance; and
- coordination of a subregional response when required.

FIGURE A2.1. Seven subregional networks established around 2001 for monitoring the efficacy of antimalarial medicines before the introduction of ACTs



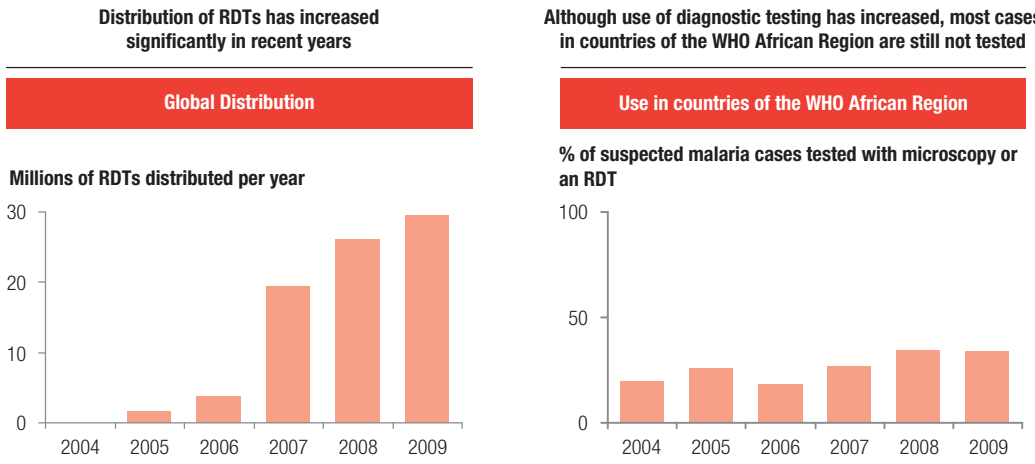
EANMAT, East African Network for Monitoring Antimalarial Treatment; HANMAT, Horn of Africa Network for Monitoring Antimalarial Treatment; RACTAP, Réseau d'Afrique Centrale des Thérapeutiques Antipaludiques; RAVREDA, Red Amazónica para la Vigilancia de la Resistencia a las Drogas Antimaláricas; WANMAT, West African Network for Monitoring Antimalarial Treatment.

In 2010, only three monitoring networks remained fully operational: the Red Amazónica para la Vigilancia de la Resistencia a las Drogas Antimaláricas, the Horn of Africa Network for Monitoring Antimalarial Treatment and the Mekong network. Each network maintains a sentinel surveillance network in its geographical area of action, provides training to support control programmes and promotes cooperation among member countries.

Annex 3. Current use of diagnostic testing for malaria

Although the availability and use of parasitological diagnosis are increasing, there are clear opportunities for improvement (Figure A3.1). Global distribution of RDTs has increased significantly, from virtually 0 in 2004 to approximately 30 million tests annually in 2009. As expected, use of parasitological diagnosis also increased during this period, and, as of 2009, approximately 35% of suspected malaria cases in endemic countries of the WHO African Region were tested by microscopy or an RDT. Despite the strong increase in the percentage of cases tested since 2004, most cases of suspected malaria in these endemic countries are still treated presumptively.

FIGURE A3.1. Availability and use of parasitological diagnosis



Source: WHO Global Malaria Programme, 2010.

Various challenges continue to prevent more widespread adoption of diagnostics:[26]

- The WHO recommendation for universal diagnostic testing of suspected malaria cases, regardless of age, was made only in early 2010.
- Distribution of RDTs tends to be poorer than distribution of ACTs, resulting in stock-outs and poor access (Renshaw et al., 2009).
- The quality and performance (sensitivity, specificity, heat stability and longevity) of RDTs varies significantly by manufacturer and by lots produced by a single manufacturer (WHO, 2010).
- Some providers and patients still believe that most fevers are due to malaria.
- Some providers and patients are unaware of the harm of treating cases without malaria with ACTs.

In some regions, patients with negative results from a diagnostic test still receive and take antimalarial medicines. For example, in Zambia in 2007, 58.4% of patients with a negative microscopy result and 35.5% of patients with a negative RDT result received an antimalarial medicines (Hamer et al., 2007). In the United Republic of Tanzania in the same year, 51% of patients with a negative microscopy result and 54% with a negative RDT result received an antimalarial medicine (Reyburn et al., 2007). In Kenya in 2010, 60% of RDT-negative patients purchased an ACT (J. Cohen, unpublished data).

[26] According to interviews conducted by The Boston Consulting Group between May and July 2010.

Non-compliance with the results of a diagnostic test may be due to a number of factors, including:

- the time required for a doctor to diagnose and treat non-malarial causes of fever;
- lack of faith in a negative diagnosis; where microscopy has been of poor quality for years, providers and patients have grown accustomed to ignoring diagnostic test results (Ansah et al., 2010); and
- lack of alternative diagnosis and treatment options for non–malarial febrile illnesses.

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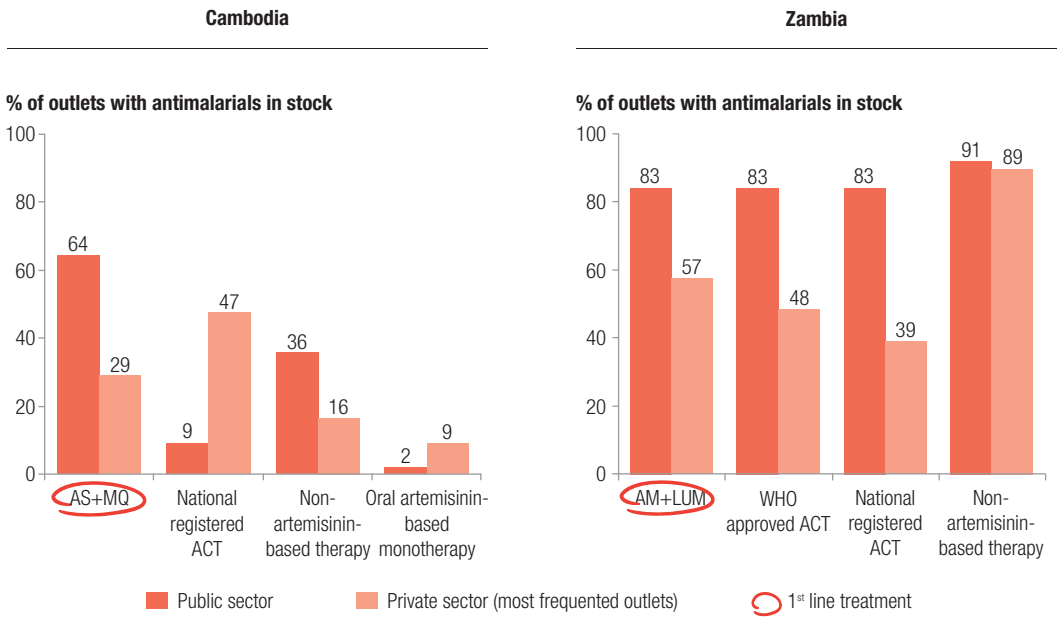
Annex 4. Current availability of ACTs in endemic countries

While access to ACTs is inconsistent in endemic countries, it has improved in countries that have made efforts to adhere to WHO *Guidelines for the treatment of malaria*. For example, in both Cambodia and Zambia, progress has been made in aligning the ACT supply with patient needs, with less frequent stock-outs of first-line treatment in the public sector (Figure A4.1). In addition, Cambodia has made significant progress towards eliminating oral artemisinin-based monotherapies, with only 2% of public sector outlets and only 9% of private sector outlets stocking them.

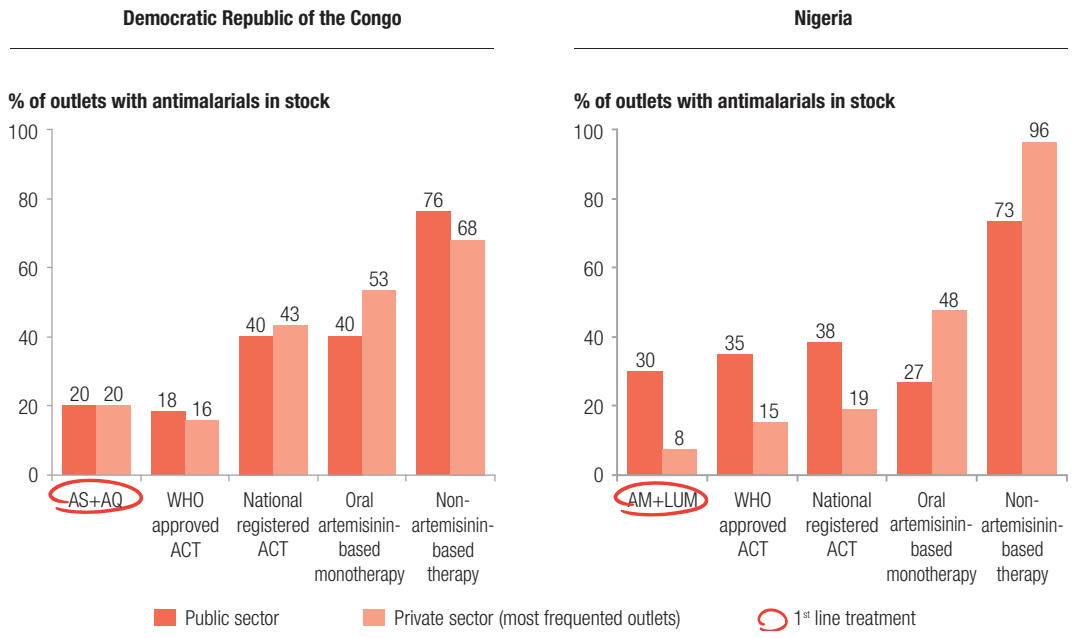
FIGURE A4.1. Availability of ACTs in Cambodia and Zambia



AS+MQ, artesunate plus mefloquine; AM+LUM, artemether plus lumefantrine.
Source: ACTwatch Outlet Survey Reports (baseline as of 2008), Population Services International.

Many other endemic countries still face challenges. For example, ACTwatch data indicate that outlets in the Democratic Republic of the Congo and Nigeria are more likely to stock other antimalarial drugs (including non-artemisinin-based therapies and monotherapies) than ACTs (Figure A4.2).

FIGURE A4.2. Availability of ACTs in the Democratic Republic of the Congo and Nigeria



AS+AQ, artesunate plus amodiaquine; AM+LUM, artemether plus lumefantrine.
Source: ACTwatch Outlet Survey Reports (baseline as of 2008), Population Services International.

Annex 5. Removal of oral artemisinin-based monotherapies

HALTING ACCESS TO ORAL ARTEMISININ-BASED MONOTHERAPIES

Since 2006, WHO has made many efforts to halt the manufacture and marketing of oral artemisinin-based monotherapies globally and locally (Table A5.1). All national malaria control programmes have removed these monotherapies from the public sector. More efforts are needed to completely phase out these medicines from the private sector in many endemic countries (R. Newman, personal communication).

In May 2010, at the Eighteenth RBM Board meeting, representatives of 40 ministries of health committed themselves to:[27]

> *"Express our governments' engagement to eliminate (ban and enforce) oral artemisinin-based malaria monotherapies and substandard ACTs from the market through tangible policies, strategies and regulatory measures within the next 12 months".*

The ministerial commitment was signed by representatives from Algeria, Angola, Benin, Botswana, Burundi, Brazil, Cameroon, Cape Verde, Chad, the Comoros, the Congo, Côte d'Ivoire, Djibouti, the Democratic Republic of the Congo, Eritrea, Gabon, the Gambia, Ghana, Guinea, India, Kenya, Liberia, Madagascar, Malawi, Mali, Mozambique, Namibia, the Niger, Rwanda, Sao Tome and Principe, Senegal, Sierra Leone, South Africa, the Sudan, Swaziland, Togo, Uganda, the United Republic of Tanzania, Zambia and Zimbabwe.

AREAS OF THE WORLD WITH PRODUCERS OF ORAL ARTEMISININ-BASED MONOTHERAPIES

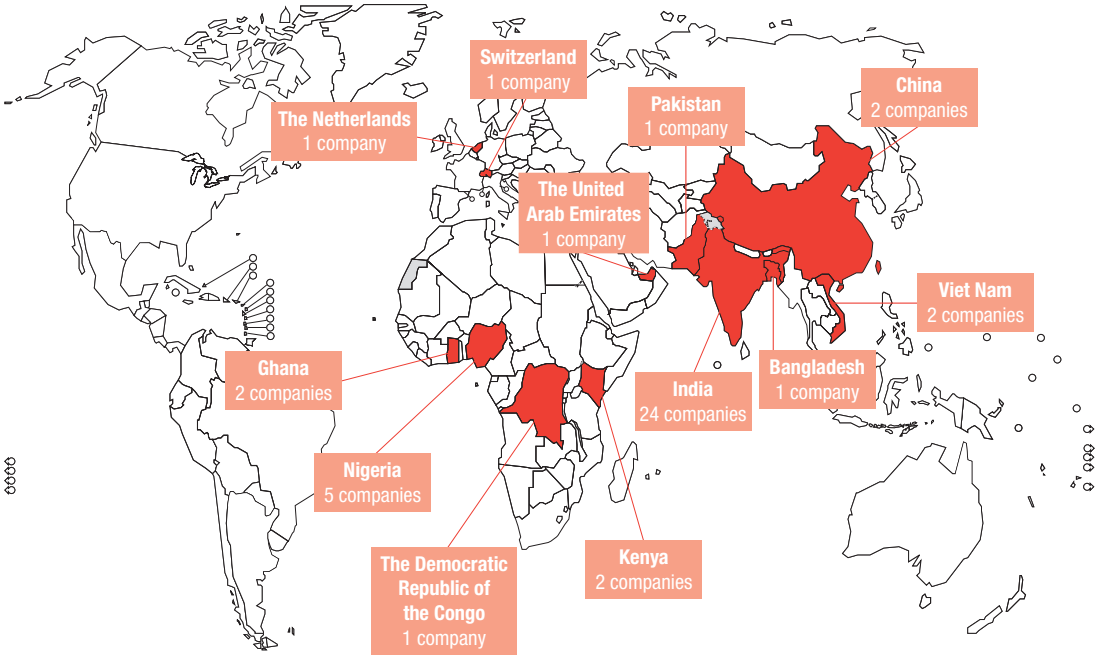
Since 2005, WHO has worked proactively with pharmaceutical companies to halt the production of oral artemisinin-based monotherapies. Initially, 76 companies were known to produce and market these products. After intensive efforts, this number has been decreased to 43 (http://www.who.int/malaria/marketing_of_oral_artemisinin_monotherapies/en/index.html). The map in Figure A5.1 shows the areas of the world in which these 43 known manufacturers are located.

[27] RBM/BOM/2010/SUB.

TABLE A5.1. WHO and RBM actions to remove oral artemisinin-based monotherapies

DATE	ACTION
January 2006	Press release calling for an immediate halt to provision of oral artemisinin-based monotherapies
January–April 2006	Web-based monitoring system regularly updated information on marketing practices and positions of national drug regulatory agencies
April 2006	Technical briefing on malaria guidelines and artemisinin-based monotherapies; meeting with pharmaceutical companies to discuss potential risks associated with the development of artemisinin resistance and to obtain commitments and a realistic implementation plan
April 2006–May 2007	Alignment of funding and procurement: joint work with funding agencies, multilateral organizations, bilateral donors and international suppliers to discontinue funding of oral artemisinin-based monotherapies and to procure only WHO-recommended medicines
May 2007	World Health Assembly resolution 60.18 urges Member States to cease the marketing and use of oral artemisinin-based monotherapies in both the public and the private sectors and to promote the use of ACTs
August 2007	Informal consultation with manufacturers of artemisinin-based antimalarial medicines to review progress and challenges in reducing reliance on monotherapies, to discuss the expected impact of new ACT funding initiatives and to agree on mechanisms of action
December 2009	WHO Global Malaria Programme submits a strategy to set out how the RBM Partnership can mitigate the risk of emerging drug resistance, including that due to use of oral artemisinin-based monotherapies
May 2010	RBM ministerial meeting at which ministers from malaria-endemic countries signed a commitment to eliminate oral artemisinin-based monotherapies from their markets

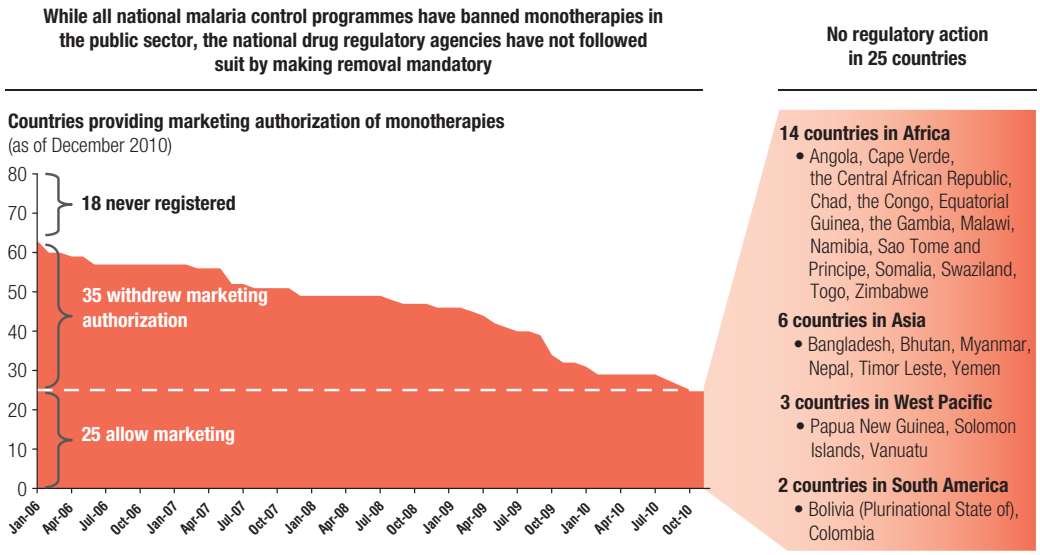
FIGURE A5.1. Areas of the world in which oral artemisinin-based monotherapies are known to be produced



MALARIA-ENDEMIC COUNTRIES THAT STILL ALLOW MARKETING AND USE OF MONOTHERAPIES

Despite efforts by WHO, RBM and other stakeholders, as of December 2010, the national drug regulatory authorities of 28 malaria-endemic countries still allowed marketing of oral artemisinin-based monotherapies for use in the private sector (Figure A5.2). Many of these countries are in regions of high malaria transmission, where artemisinin resistance could spread quickly once introduced. Even in countries where action has been taken to remove these products, enforcement remains a significant challenge.

FIGURE A5.2. Current situation of removal of marketing authorization for oral artemisinin-based monotherapies



Source: WHO Malaria Global Progam, December 2010.

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ISBN 978 92 4 150083 8