Joint Assessment of the Response to Artemisinin Resistance in the Greater Mekong Sub-Region

Conducted November 2011 to February 2012

Summary Report

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World Health Organization
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Preface

This Joint Assessment was initiated by AusAID, DFID, USAID and the Bill & Melinda Gates Foundation, agencies involved in the funding of malaria control in the GMS and more widely that are highly concerned by the emergence of artemisinin resistant malaria and the impact that this may have on regional and global efforts to control and eliminate this disease. This Joint Assessment Report will feed into the regional Mekong Response to Artemisinin Resistance Framework currently being prepared under the coordination of WHO.

The Joint Assessment Team included four independent consultants and three staff from WHO, which efficiently coordinated all country visits and communication with stakeholders.

This assessment would not have been possible without the open and enthusiastic collaboration of the concerned National Malaria Control Programmes (NMCPs) and their many partners in programme implementation and in research. The Joint Assessment Team wishes to express its gratitude to them all.

Visits to countries were short and inevitably the team will have made some errors in its assessment, for which we apologize.

Contents

ABBREVIATIONS

ACT	Artemisinin-based combination therapy
AMFm	Affordable Medicines Facility for malaria
BCC	Behaviour change communication
BMGF	Bill and Melinda Gates Foundation
DHA-Pip	Dihydroartemisinin and piperaquine
G6PD	Glucose 6 Phosphate Dehydrogenase enzyme
GFATM	Global Fund to Fight AIDS, Tuberculosis, and Malaria
GMS	Greater Mekong Sub-Region
IEC	Information, education, communication
IRS	Indoor residual spraying
ITN	Insecticide-treated net
LLIHN	Long-lasting insecticide-treated hammock net
LLIN	Long-lasting insecticide-treated net
MMP	Mekong Malaria Programme
MOH	Ministry of Health
MRA	Medicine regulatory agency
NGO	Non-governmental organization
RBM	Roll Back Malaria
RDT	Rapid diagnostic test
SEARO	South-East Asia Regional Office
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development
VMW	Village Malaria Worker
WHO	World Health Organization
WPRO	Western Pacific Regional Office

1. Introduction

ACTs have become one of the most powerful tools in controlling malaria globally, contributing to real progress. The emergence of artemisinin resistance in the Greater Mekong Sub-region[1] (GMS) is therefore a matter of grave concern, given the lack of good alternative drugs and the history of resistance to other drugs, first detected in the same region, eventually appearing everywhere and coinciding in Africa with increased mortality. There is an opportunity, through effective and timely action, to protect the progress made in recent years.

This report is of a Joint Assessment of the Response to Artemisinin Resistance in the GMS conducted between November 2011 and February 2012 through review of documents, attendance at several key technical meetings and visits to Cambodia, China, Myanmar and Vietnam, including to areas affected by artemisinin resistant malaria. Information for Thailand and Lao PDR was collected from existing documents and some limited interviews.

This exercise does not pretend to be a thorough review of the national malaria control programmes (NMCP) in the countries visited. These have been extensively documented elsewhere. The aim was to focus on policies, plans and actions of particular relevance to the response to artemisinin resistance.

This summary report has five sections. Following the introduction (Section 1), Section 2 sets out summary findings and recommendations of the assessment team. Section 3 describes the context in which artemisinin resistance is being tackled. Section 4 highlights key achievements and enabling factors for the response to artemisinin resistance, whilst Section 5 provides a more detailed discussion of major issues to be addressed. A more detailed report has been prepared, which is available on request.

2. Summary findings and recommendations

This assessment has found that a good, if delayed, start has been made to addressing artemisinin resistance in the GMS. In some areas the impact has already been impressive. In general the approach outlined in the Global Plan for Artemisinin Resistance Containment (GPARC) and several associated national level strategies and plans is appropriate. It is acknowledged that national strategies are, with the exception of those of Cambodia and Thailand, in their early stages of implementation. However, overall the assessment is sobering. It is impossible to avoid the conclusion that not enough is yet being done, with enough intensity, coverage and quality, to respond to a problem that could not only slow future progress but also undo the gains already made in malaria control worldwide.

This report calls for a very large increase in attention to this issue. Inadequate investment of money, other resources, effort and coordination now will not achieve the goal of limiting artemisinin resistance, and the costs of failure to do so are likely to be high in human lives and financially.

When the initial response strategy for Cambodia and Thailand was developed, a key challenge was to decide on its geographic scale. Data on confirmed resistance were limited, and data on confirmed absence of resistance were similarly limited. There were already concerns that artemisinin resistance might be in Myanmar, and that the higher transmission there meant greater risks of expansion. However, there was no evidence, and limited access to work there. The cost of operations even in small parts of Cambodia and Thailand was already estimated to be very high considering the low burden of disease compared to much of Africa, so containment activities were kept relatively limited.

The approach was to try to eliminate all *P. falciparum* cases in areas of known resistance. This strategy was rational, but now that resistance has been confirmed outside the original area as far as the Thai-Myanmar border and Vietnam, it will be important to continue research to distinguish between

[1] Greater Mekong Sub-region includes Cambodia, Lao PDR, Myanmar, Thailand, Vietnam and Yunnan Province of China

independent emergence of resistance versus spread from a single focus. If the latter occurs, there may be a need to consider how the strategy could be adapted.

Although the confirmation of slow parasite clearance in areas outside the original containment zones necessitates some review of the overall strategy, most of the activities in the strategy are applicable for a goal of interrupting local artemisinin-resistant *P. falciparum* transmission, even if resistance is occurring in other areas. As it is still not certain whether the new foci of resistance resulted in spread from a single original focus, the most pragmatic approach is to make sure activities cover as wide an area as possible around known foci of resistance.

Five of the countries of the GMS have declared an intention to move progressively towards the complete elimination of malaria. It is important to recognize that an aggressive response to artemisinin resistance supports rather than competes with efforts towards malaria elimination. Both require rigorous, high quality implementation of proven malaria control interventions. The field response to artemisinin resistance differs from the longer-term elimination activities in urgency and geographical focus. It can serve to refine approaches that can then be applied to elimination, including, potentially, the development of new approaches to detecting and responding to residual foci of malaria.

The joint assessment has, inevitably, identified a long list of issues – areas where new, more or better action is needed for an effective response to artemisinin resistance. Each of these issues could lead to one or more recommendations, many of which would have been made before, indeed by groups more expert in various areas than this assessment team. The intention here is not to do that but to identify a short list of areas in which issues need to be addressed as a matter of priority and with some sense of urgency.

Each of these areas is expanded below. Each area will need agreement on a plan of action by key stakeholders – mostly, if not fully, incorporated into the Mekong Response to Artemisinin Resistance Framework currently being developed under WHO's coordination. Not all areas require waiting for the Regional Framework to be launched and operational. Action is required in some areas immediately. Ten fields of priority action are proposed.

1. Intensify current field operations and manage them for results.

Rationale: Overall current response to artemisinin resistance operations and their management are not at a level of intensity and rigour compatible with the effective control of a major public health threat.

Priority actions are listed below, but clearly these are not the only things that need to be done. Effective response to artemisinin resistance can only be achieved if built on a base of good quality malaria control, including in areas outside the priority geographic tiers.

The geographic foci of intensification of operations and the tiers on which they are based may need to be updated and, potentially, significantly and rapidly expanded as new information becomes available.

Management:

- Clearly define roles of all levels (especially at different levels within countries);
- Collect and use quarterly programme implementation data to manage operations;
- Ensure regular supportive supervision at all levels;
- Do not allow supply stock-outs of essential commodities to occur;
- Manage incentives to motivate staff for highest performance;
- In countries with a malaria elimination strategy, link the approach and management of the response to resistance to the elimination efforts to ensure complementarity, while ensuring that an urgent focus on addressing resistance is not lost.

Interventions:

- Ensure 100% coverage of key interventions (prevention, diagnosis and treatment) in priority geographic areas Tiers 1 and 2 (see Box 3, page 14). Intensify malaria control in **all** malarious areas. Develop systems to maintain high coverage;
- Apply more widely lessons from Cambodian experience with village malaria workers.

Surveillance and M&E:

- Continuously use detailed surveillance data to identify problems and target operations in Tiers 1 and 2. Progressively move to using data on each malaria case;
- Refine approaches to active surveillance **and response** in low transmission areas and with migrant/mobile populations;
- Optimize the use of modern information technology to improve surveillance and rapid response;
- Fully use agreed monitoring and evaluation frameworks based on routine and survey data.

2. Strengthen leadership as well as coordination and oversight mechanisms

Rationale: Regional leadership and, in most GMS countries, coordination of response to artemisinin resistance activities undertaken by multiple partners is inadequate.

- Ensure all countries have an established group for coordinating the response to artemisinin resistance that meets regularly, defines action points and follows-up;
- Ensure WHO has financial and human resources to play its role effectively;
- Expect WHO to place staff with appropriate skills, in adequate numbers, across the GMS, including for programme management where this is required;
- Explore cost-efficient roles for other technical partners under overall WHO leadership;
- Consider whether there is a need for a small adequately resourced regional coordination group and if so its roles, affiliations and location. The advantage of WHO leading such a group is its mandate and access to health authorities in countries. The advantage of such a group being based in Bangkok is ease of travel to affected countries;
- Establish a small independent group to monitor and advise the response to artemisinin resistance across the GMS.

3. Secure adequate financial resources

Rationale: Current spending on the response to artemisinin resistance is grossly inadequate and the financial difficulties of the GFATM are having a massive impact on available funding.

- Stakeholders coordinate efforts to fill the five-year funding gap of $150 million. Currently funding uncertainty is greatest for operations in Myanmar and Vietnam, for coordination and research;
- Lobby to increase domestic resources;
- Development partners advocate for more resources at regional and global level;

- Assess and plan for consequences of GFATM financial constraints;
- Consider emergency reserve funds to allow more rapid start-up of response efforts in new areas. Currently funding uncertainty is greatest in Vietnam and Myanmar.

4. Build political support

Rationale: Political awareness/endorsement of malaria elimination appears to be high. The same may not be true for the response to artemisinin resistance, which is essential for malaria elimination. Without political support there will be inadequate resources.

- Influential stakeholders seek to build political awareness of the importance of artemisinin resistance in concerned countries and regionally/globally;
- Continue to build political support through ASEAN, SAARC, APEC and WHO global and regional bodies;
- Affected countries to use regional organizations and bodies to advocate for an effective response to artemisinin resistance and to secure cooperation on regional agreements;
- Where appropriate, lobby for action on artemisinin resistance in the context of health security;
- Sensitise leaders outside of the GMS, including those in Africa, to the future threat;
- Use media to build political awareness.

5. Clarify and implement policy decisions on diagnosis and treatment

Rationale: National treatment guidelines will have an impact on artemisinin resistance beyond national borders. Rational policy decisions require rigorous implementation.

- Clarify and disseminate policy on interim use of atovaquone-proguanil (Malarone™) in Thai-Cambodia border areas;
- Develop plans to expand the use of primaquine in *P. falciparum* treatment once safety issues have been clarified; support countries with the implementation of existing policies on use of primaquine;
- Anticipate and address possible issues with the introduction of artesunate-pyronaradine;
- Promote policy of all treatment being preceded by parasitological diagnosis, including in the private sector;
- Seek passage of laws and take other measures to eliminate use of artesunate monotherapy in the private sector in all countries.

6. Maintain, expand and improve drug efficacy surveillance networks

Rationale: Excellent and well-coordinated Therapeutic Efficacy Studies (TES) have been carried out across the GMS complemented by other efforts to understand and track resistance. This needs to continue and expand to new areas. This work underpins the response to artemisinin resistance action.

- Ensure that the GMS TES network is maintained and operates according to agreed standards under WHO coordination. Intensify TES in countries neighbouring the GMS, in Africa and elsewhere;

- Ensure links between NMCPs and research institutions to conduct additional studies (*in vitro*, molecular markers, pharmacokinetic) to complement TES.

7. Accelerate priority research

Rationale: Progress on some critical research issues has been very slow. A well-prioritized and coordinated agenda would help resolve such issues quickly.

- Ensure WHO convenes informal meetings between researchers and NMCP managers to agree on (a) the priority research agenda, and (b) mechanism to coordinate research and sharing of data;
- Charge a small expert group with managing a "fast-track" research agenda. This may be the Technical Expert Group on Drug Resistance that has been requested by the Malaria Policy Advisory Committee;
- Allocate adequate and flexible funding;
- Highest priority issues to address should include:
    - Primaquine/G6PD related issues;
    - The search for a molecular marker of resistance;
    - Highly sensitive diagnostic tools;
    - Behavioural research in key risk groups;
    - Effectiveness of innovative prevention tools;
- Clearly define the role of Day 3 parasitaemia surveillance, issue detailed Standard Operating Procedures, test response strategies and monitor closely;
- Support collaborative research efforts to maximize use of resources, skills and samples.

8. Target migrant and mobile populations and engage with relevant employment sectors

Rationale: All countries of the GMS have identified certain populations as being the main reservoirs of malaria cases and/or of being particularly difficult to address with control measures. The populations are linked to particular socio-economic activities such as mining, forestry, plantation work, construction of roads, dams, hydro-power, etc., that employ many (both border-crossing and internal) migrant workers.

- Focus on migrants and mobile populations (including seasonal workers) and other groups exposed by occupation (including military);
- Seek to understand who gets malaria, where and why (occupational or living style risks) engaging not just epidemiologists but also social scientists;
- Proactively test innovative approaches to malaria prevention and treatment in these populations, including through transit route or work site interventions working with labour organizers, employers and others;
- Engage other relevant sectors for effective control of malaria among migrant workers to reduce the risk of emergence and spread of artemisinin resistance.

9. Prioritize Myanmar (while maintaining a strong response to artemisinin resistance in all GMS countries)

Rationale: Myanmar accounts for 78% of malaria cases and 75% of malaria deaths in the GMS, has the most under-resourced health system and is a potential conduit for amplification and spread of resistance to the West.

- Recognize that Myanmar requires special and urgent additional attention;
- Take advantage of thawing relations to significantly increase external support;
- Very substantially increase support for WHO in Myanmar given its unique role in managing resources and staff on behalf of the NMCP;
- Ensure Vietnam receives support in the short-term to expand its response to artemisinin resistance.

10. Engage with the pharmaceutical sector

Rationale: Major issues related to the manufacture and sale of anti-malarial drugs cannot be addressed without a concerted regional effort involving the pharmaceutical sector.

- Consider establishing a regional pre-qualification mechanism for antimalarial drugs to expedite approvals;
- Work to overcome current bottlenecks in pre-qualification that would allow regional producers of ACT to supply the international market (and stop producing artemisinin monotherapy);
- Work to ensure all ACT products manufactured or traded in the GMS are of high quality, in the context of growing regional interest in ensuring access to quality medicines and rational use of antimicrobials;
- Work towards an enforceable regional agreement banning the sale and export of artemisinin monotherapy;
- Work with the ASEAN Working Group on Pharmaceutical Development on these issues;
- Encourage and support the pharmaceutical industry in Asia to continue research to develop next generation non-artemisinin-based antimalarial drugs.

Box 1: Why invest in responding to artemisinin resistance now?

Recent progress and future hope in reducing malaria mortality are built on ACT

Between the 1980s and the 1990s malaria mortality in children in Africa, where most malaria deaths occurred, increased by 80%. At least in part, this was associated with growing resistance to the antimalarial drugs then used. Following considerable scale-up of malaria control and the progressive introduction of ACT in African countries the situation dramatically improved; global malaria-specific mortality fell by a quarter from 2000 to 2010. ACT is now the mainstay of treatment for *P. falciparum* malaria worldwide. The Global Malaria Action Plan includes a goal of near-zero malaria deaths globally by 2015 based in part on the hope offered by ACT.

Loss of ACT as an antimalarial would bring huge loss of life

In 2010, almost 600,000 deaths occurred in Africa (91% of the global total). By that time the malaria-specific mortality rate in Africa had fallen by 33% compared with 2000, in part due to the use of ACT. The proportion of malaria cases treated with ACT in 2010 and its contribution to reducing mortality are unknown. However, assuming that at least 200,000 malaria deaths were averted by all measures in Africa in 2010, even a 25% contribution attributed to ACT would represent a minimum of 50,000

deaths. Plausibly, therefore, the additional deaths that could be expected to occur annually if ACT had to be abandoned before a new anti-malarial drug became available would be in the tens of thousands. Such an impact would not necessarily be immediate. It took some ten years for chloroquine resistance to spread across Africa and resistance to ACT may emerge more slowly. But links between Africa and Asia, where evidence of resistance to artemisinin and some of its ACT partner drugs already exists, are far greater than in past decades and growing fast. It cannot be assumed that we will have a buffer of time to deal with artemisinin resistance if it emerges in Africa.

There is currently no practical alternative to ACT

No other drug regimen is currently available that could replace ACT. Atovaquone-proguanil, an effective non-ACT drug mostly used for prophylaxis in travellers, is expensive and it is expected that resistance to it would develop rapidly, within 1-2 years of widespread use. Its use would require directly observed treatment, which is practically difficult. Another alternative, quinine and tetracycline (or doxycycline), requires an impractical 84 tablets (56 if doxycycline is used) over seven days for an adult treatment and is not recommended for children under 8 years or pregnant women. New non-ACT drugs are in the research and development pipeline but if one or more were proven to be safe and effective they would not be available for wide-scale use in less than five years, as a minimum.

Loss of ACT = Economic loss

While most malaria cases are not fatal the human and economic costs of malaria are significant. For children, frequent illness affects growth and development and school attendance, for adults work productivity; all have an economic cost. In addition, the out-of-pocket costs of failing treatment, which often entails repeated journeys to seek treatment, can be catastrophic for poor people. Costs of diagnosing and treating malaria range from $2-24 for uncomplicated malaria and $16-138 for hospitalized cases. The median cost-effectiveness ratio for treatment with ACT has been calculated at $25 per DALY averted[2], which is highly cost-effective, and has been shown to be higher than for other antimalarials. Loss of ACT as a standard treatment for malaria may lead to more frequent illness requiring more expensive and less cost-effective drugs. Total expenditure on drugs may increase significantly, whether from the patients' pockets or government budgets. Frequent changes in standard treatment guidelines incur high costs for the recall of drugs, development of new guidelines, retraining of staff and public education. Extending the useful life of a drug avoids these costs and increases the return on the investment in its development. The perceived risks of a drug-resistant form of malaria may have a significant impact on tourism and associated revenue in affected countries. Also, an increase in multi-drug resistant malaria may undermine confidence in the target of malaria elimination, leading to decreased investments and consequent losses on those already made.

Clearly, the estimation of the economic costs of not responding to artemisinin resistance would be a complex exercise, and is beyond the scope of this assessment, but it seems apparent that they would far out-weigh the costs of enhanced malaria control in what are still a limited number of geographic foci of resistance. There is little to lose by investing in a major effort to respond to artemisinin resistance. It is an investment in good malaria control and it can strengthen systems and improve the quality of operations increasing the progress towards elimination of the disease while existing affordable tools remain effective.

The economic returns on good malaria control are impressive. Recent studies have suggested that accelerating investments by 10% per year over five years could increase annual gross domestic product in Africa by more than $20-30 billion due to increased productivity and growth of foreign investment. In one region of one country alone (Tigray in Ethiopia) it was estimated that sustained malaria control over the next five years could avert about $427 million in household costs equivalent to 8% of household income. These impressive potential savings are fragile; they depend on the efficacy of current malaria control tools.

[2] White, MT, Conteh L, Cibulskis R, Ghani A. 2011. Costs and cost-effectiveness of malaria control interventions – a systematic review, Mal. Journal 10: 337

3. The context

Dedicated and structured efforts to combat artemisinin resistance are relatively recent, starting with the Cambodia-Thailand Artemisinin Resistance Containment project in 2009. This assessment encountered national responses to artemisinin resistance efforts at very different levels of development and implementation. Nevertheless, there has already been significant impact. Malaria has been reduced to low levels, for example, in the Thai-Cambodia border area. In general, this summary report focuses more on issues that could affect the progress of the response to artemisinin resistance in the future than on achievements to date.

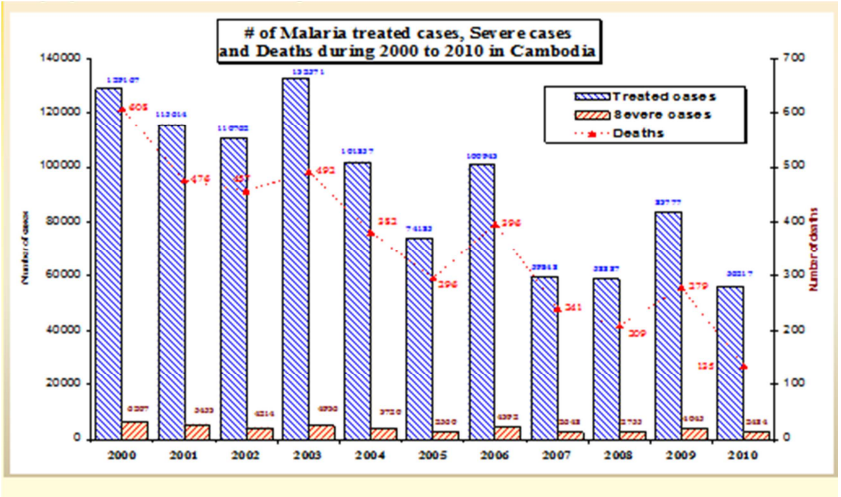
3.1 Progress in malaria control

In all countries of the GMS there has been an increased commitment to malaria control over the past decade. All countries have endorsed the WHO South East Asian and Western Pacific regional strategic plans for malaria control and elimination, and all countries have made significant progress in reducing the malaria burden, in many areas to very low levels. There is a commitment to moving towards elimination of malaria in all countries except Myanmar, which accounts for three-quarters of malaria cases and deaths reported in the GMS and where aiming for elimination may be premature. In Cambodia the Prime Minister initiated the drive for elimination and in other countries it has high-level endorsement.

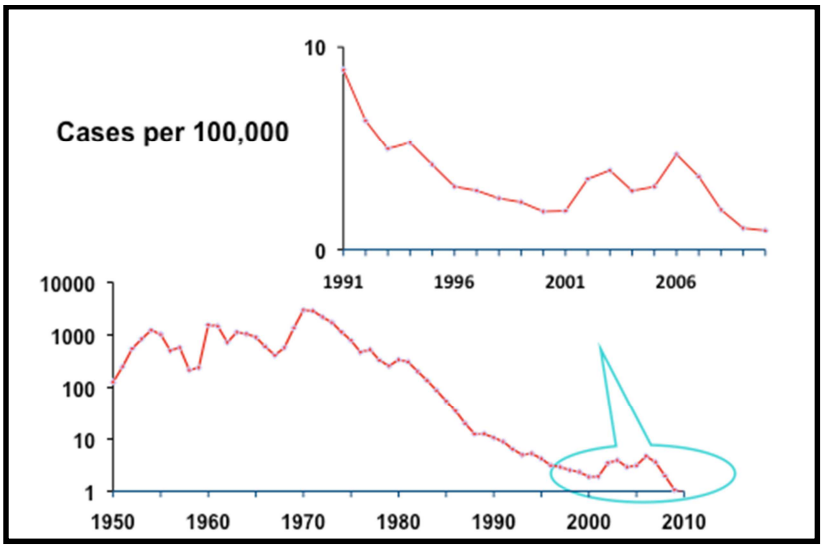
As can be seen in set of graphs presented in Figure 1, there has been a significant reduction in overall malaria incidence in all countries since 1990, a trend that has continued after 2000. In the last five years for which data are available the decrease in the number of confirmed cases has been less marked. In part this can be explained by the widespread use of rapid diagnostic tests (RDTs) and improving quality and coverage of microscopy with consequent increase in confirmed cases and a reduction in reporting of non-confirmed cases.

Figure 1. Trends in malaria cases and deaths in countries of the Greater Mekong Sub-region

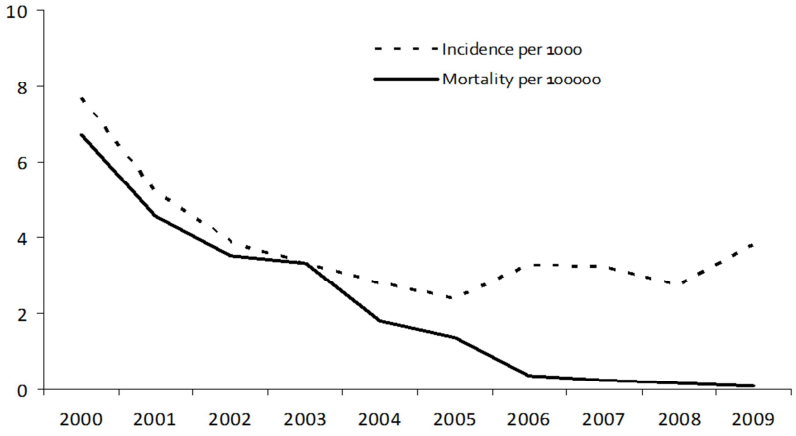
CAMBODIA – TREATED CASES and DEATHS, 2000-2010



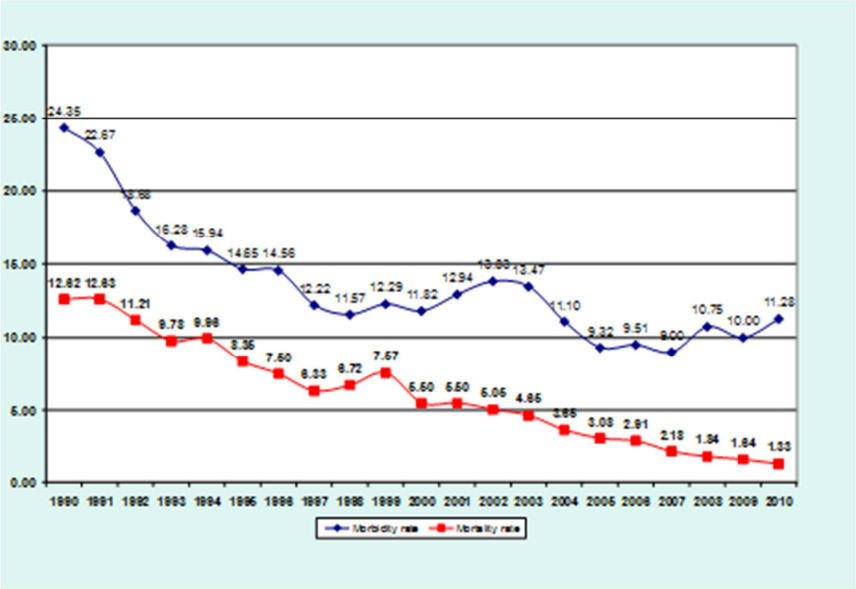
CHINA – MALARIA INCIDENCE RATE, 1950-2010



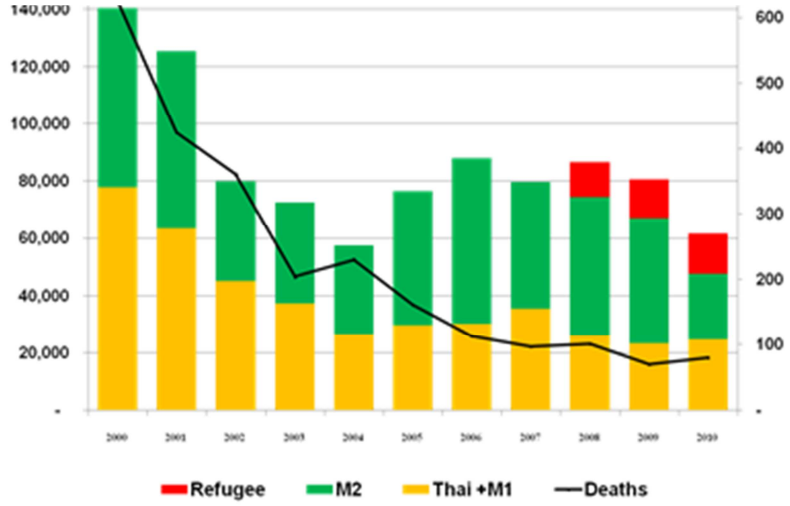
LAO PDR –INCIDENCE OF CONFIRMED MALARIA CASES and MORTALITY RATE OF PROBABLE AND CONFIRMED MALARIA, 2001-2009



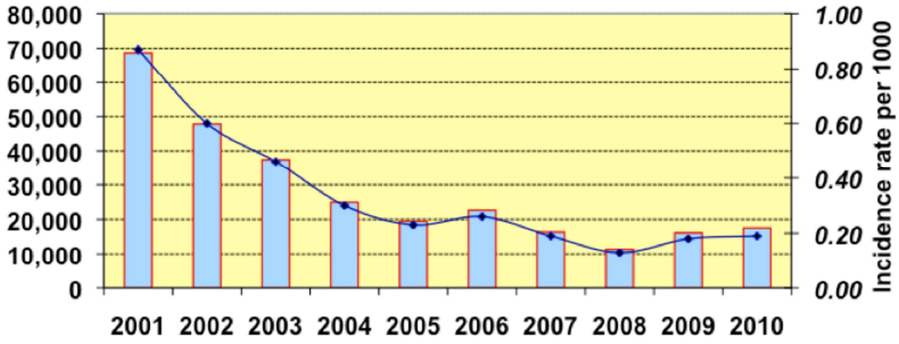
MYANMAR – MORTALITY and MORBIDITY RATES, 1990-2010



THAILAND – CASES and DEATHS, 2000-2010



VIETNAM – CONFIRMED CASES and INCIDENCE RATE, 2001-2010



Source: National Malaria Control Programmes

All countries of the GMS have well-developed national malaria control (and in some cases, elimination) strategies, some of which are undergoing revision. Five countries have declared an elimination goal each with a different timeframe. All countries have developed surveillance, monitoring and evaluation frameworks as part of their national monitoring and evaluation plans and as part of their application for The Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) funding. In addition to the national programmes, since the early 1990s considerable effort has been made to coordinate malaria control across the GMS and to facilitate collaboration, especially in border areas.

Artemisinin resistance is, therefore, being addressed in a context where efforts to control/eliminate malaria have been intensified. This is, however, also happening in a context of inadequate resources being available or allocated to fully implement the specific strategies and plans in response to artemisinin resistance that have been initiated in Cambodia, Myanmar, Thailand and Vietnam, or to achieve the coverage and intensity of interventions needed for malaria elimination.

3.2 The emergence of artemisinin resistance

Current geographic foci of artemisinin resistance, and therefore of the response to artemisinin resistance, share many characteristics. They are mostly forested (or previously forested) areas, usually along national borders far from the capitals, with significant mobile populations (internal and external migrants and seasonal workers) and health service coverage that is less than the national average. In several cases they are, or have been, zones of conflict and military presence. There is a highly efficient vector species, *Anopheles dirus*, and human populations who often have low immunity. These factors combine to make artemisinin resistance operations more challenging. The early appearance of resistance to previous antimalarial drugs in several of the same areas indicates that this environment is particularly conducive to fostering resistance development, and the genetic history of the parasites may facilitate resistance to newer drugs.

With the emergence and spread of resistance to a number of anti-malarial drugs since the 1950s and as a result of continuous research efforts to find alternative drugs, standard treatment for uncomplicated *P. falciparum* malaria worldwide has now shifted to the use of artemisinin-based combination therapy (ACT). Preservation of ACT as the effective first-line treatment for uncomplicated malaria is critical in part because there is currently no practical alternative treatment. Development and spread of resistance of malaria to artemisinin could be disastrous for global efforts to control and eliminate malaria. In order to lessen the risk of this occurring, artemisinin monotherapy is no longer recommended as treatment for uncomplicated malaria. Unfortunately, artemisinin monotherapy is still used by high numbers of patients seeking treatment in the private sector. It is likely that it is rarely taken for the full seven-day course of treatment that is needed for it to be effective.

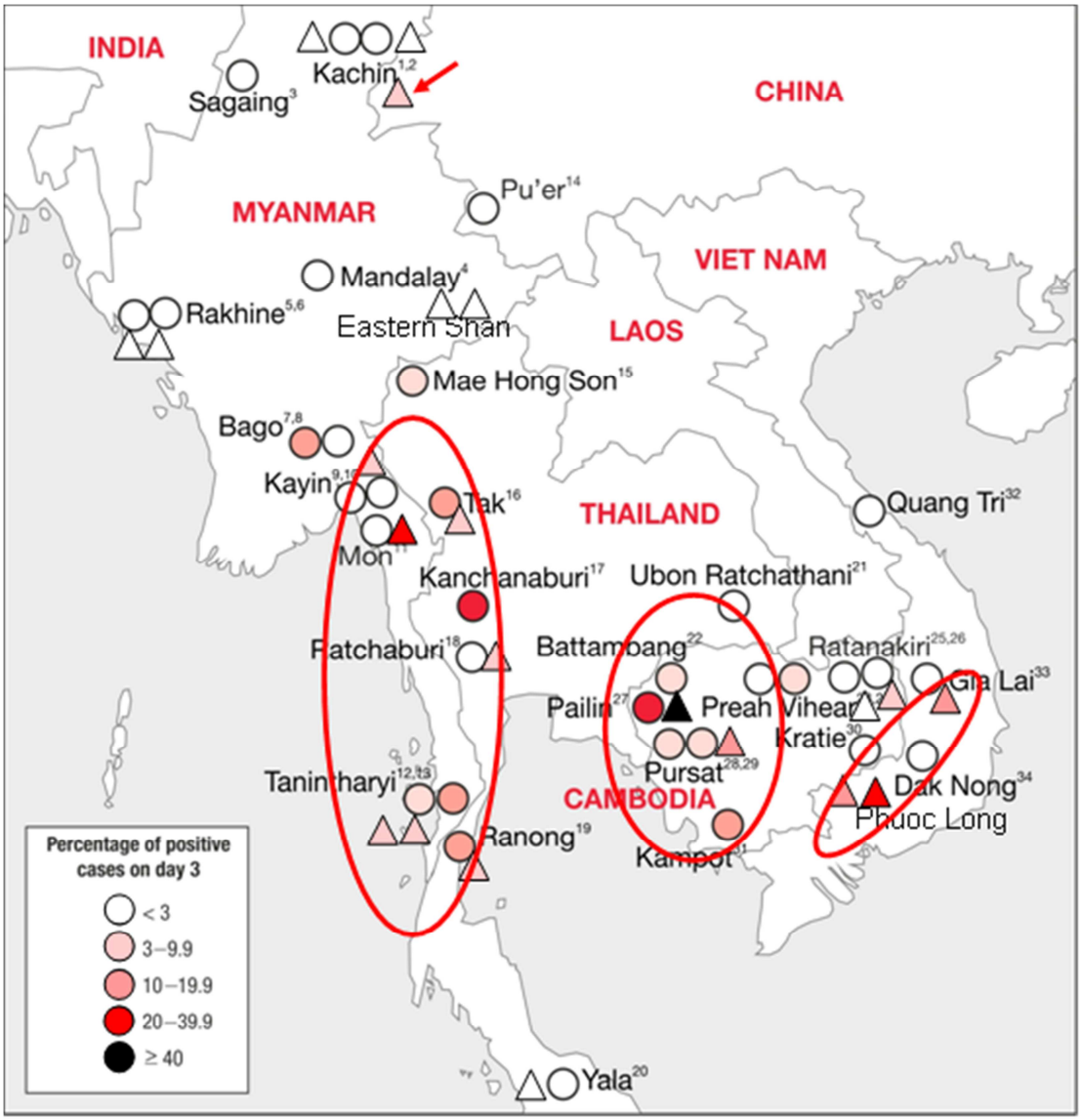
The widespread use of ACT, often without prior diagnosis, and the lack of adherence to the full 3-day treatment are putting the component drugs at risk to the emergence of resistance, especially to the partner drug. If the efficacy of the partner drug diminishes (or if resistance to it already exists) there is an increased risk that the efficacy of artemisinin will also diminish. The exposure of parasites to sub-therapeutic doses of artemisinin is increased by the presence of sub-standard or counterfeit drugs. Recrudescence of parasitaemia following such treatment may have a high proportion of resistant parasites and if not treated in a timely way can contribute to the spread of resistance. The first signs of resistance to artemisinin have now been detected in four countries of the GMS as shown in Figure 2.

Historically, the GMS has been the starting point for the emergence of resistance to anti-malarial drugs that were the cornerstones of malaria control and the sub-region has an active network conducting therapeutic efficacy surveillance complemented by laboratory testing and research studies. An expanding body of data has allowed mapping of the geographical extension of artemisinin resistance and, potentially, will contribute to an understanding of its mechanisms. Figure 2

summarizes data on Day 3 parasitaemia (as a marker for artemisinin resistance) detected across the GMS.

Factors that may favour the emergence or spread of artemisinin resistance include overuse of drugs following presumptive diagnosis, use of monotherapy, lack of adherence, under-dosing in some age groups, sub-standard or counterfeit drugs, lack of follow-up to detect treatment failure, failing partner drugs, and the presence of populations particularly liable to spread resistant parasites, including mobile and migrant populations and non-immune people visiting high transmission areas.

Figure 2. Percentage of cases with Day 3 parasitaemia after ACT (Circles represent data before November 2010, and triangles represent data after November 2010)



Source: WHO Global Malaria Programme, 2012

Box 2: Definitions of artemisinin resistance and challenges of Day 3 parasitaemia surveillance

Working definitions of artemisinin resistance included in the GPARC are based on clinical and parasitological outcomes observed during routine therapeutic efficacy studies (TES) of ACTs and clinical trials of artesunate monotherapy.

Suspected resistance is defined by an increase in parasite clearance time, as evidenced by >= 10% of cases with parasites detectable 72 hours after treatment with an ACT (also referred to as Day 3 parasitaemia).

Confirmed resistance is defined by 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.

Day 3 parasitaemia has not been shown to correlate well with *in vitro* artemisinin susceptibility testing, possibly due to limitations of the *in vitro* assay techniques currently used. Similarly, treatment outcomes following artesunate monotherapy and ACT do not correlate with Day 3 parasitaemia. Multi-year data from Thailand, for example, show Day 3 parasitaemia to have poor sensitivity and poor positive predictive value for artesunate-mefloquine treatment failure. Nevertheless, Day 3 parasitaemia is the best available proxy indicator for artemisinin resistance at the time of writing this report. The 10% Day 3 parasitaemia prevalence to define suspected resistance was set by consensus of a group of experts participating in the ARC3 project.

There is a growing interest in conducting Day 3 parasitaemia studies, partly because they are seen as an easier and less expensive alternative to TES. A study in Cambodia in 2011[3] of three different approaches to Day 3 parasitaemia data collection raised, however, a number of issues about the feasibility and cost-benefit of collecting such data in various settings. The interpretation of Day 3 parasitaemia prevalence and trends is also not straightforward; it can be affected by the initial parasitaemia level, accuracy of microscopy, drug pharmacokinetics and the effects of the ACT partner drug, host immunity and hemoglobinopathy status and the precise timing of the Day 3 blood specimen collection.

For data from Day 3 parasitaemia surveillance to be useful a standard protocol should be followed that assures:

- adherence with the 3-day treatment regimen, verified by directly-observed treatment;
- blood slides on Day-0 and on Day-3 (at 72 hours, not less, from initiation of treatment);
- quality assured microscopic diagnosis.

These requirements cannot always be achieved under field conditions.

Day 3 parasitaemia data collection may be useful, not only in Tier 1 and 2 areas to detect possible extension of resistance, but also in Tier 1 areas to define targets for intervention such as focal screening and treatment (FSAT) or mass screening and treatment (MSAT). Ideally, patients should also be followed for the treatment outcomes 28/42 days later; this may not be feasible, however, outside of a TES setting and may be costly.

At this stage Day 3 parasitaemia should still be considered to be within the scope of research and conducted with rigorous adherence to standard procedures, rather than as a routine programme activity.

[3] Report to Cambodia NMCP, Jonathan Cox, 2011

3.3 Overview of efforts to-date to respond to artemisinin resistance

The Global Plan for Artemisinin Resistance Containment (see Box 3) launched in 2011 provides the strategic framework for both global and national action. Cambodia and Thailand initiated artemisinin resistance containment programmes in 2009. Implementation of artemisinin resistance strategies is relatively recent in Myanmar starting in 2011 and in Vietnam in 2011.

Box 3: The Global Plan for Artemisinin Resistance Containment (GPARC) 2011

GPARC was officially launched in January 2011. Its development, coordinated by the WHO Global Malaria Programme, with funding from the Bill & Melinda Gates Foundation involved consultation with many stakeholders. It "sets out a high-level plan of attack to protect ACTs as an effective treatment for *Plasmodium falciparum* malaria". It aims to contain or eliminate artemisinin resistance where it already exists, and prevent it where it has not yet appeared. It proposes five areas of action:

- Stop the spread of resistant parasites;
- Increase monitoring and surveillance to evaluate the artemisinin resistance threat;
- Improve access to diagnostics and rational treatment with ACTs;
- Invest in artemisinin resistance-related research; and
- Motivate action and mobilize resources.

For the response to artemisinin resistance the GPARC proposes that countries divide their territory into three tiers:

- Tier I areas where 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.

In all tiers, good malaria control should comprise:

- 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); and
- Vector control, as locally appropriate, to lower transmission and minimize the spread of resistant parasites.

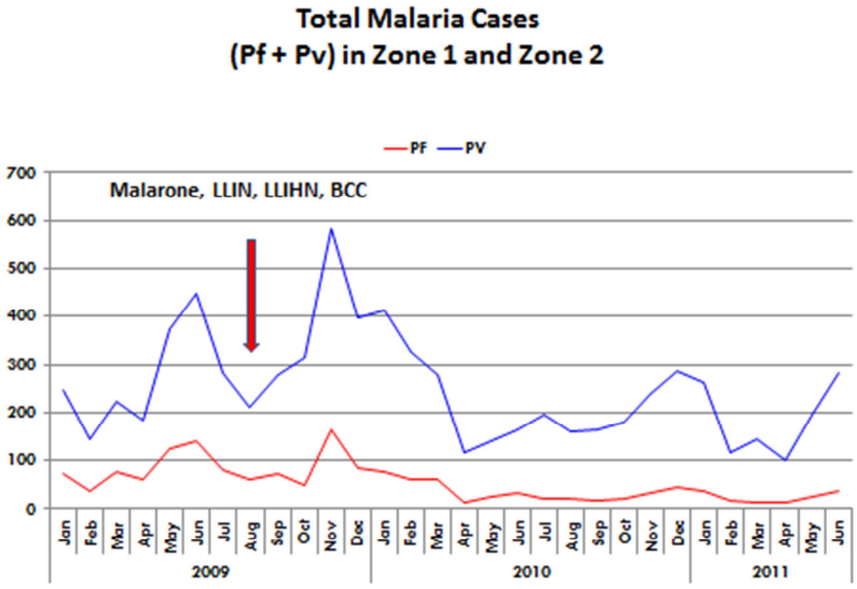
In Tier I areas it is important to move to universal coverage of these elements as quickly as possible. Tier II areas should intensify malaria control activities including these elements. In Tier III areas, while the risk of resistance is lower, every effort should be made progressively to expand coverage with these basic malaria control practices. For Tiers I and II GPARC proposes additional specific activities to contain or eliminate resistant parasites, in Tier I as quickly as possible through an immediate and multifaceted response. In Tier II the aim is to reduce transmission and/or limit the risk of emergence or spread of resistant parasites.

The four countries that have initiated response to artemisinin resistance programs have closely followed the overall GPARC strategy.

China and Laos have not launched responses to artemisinin resistance strategies as they do not yet have evidence of artemisinin resistance. China, however, supports relevant activities on both sides of its border with Myanmar. Progress by NMCPs and partners on the implementation of a response to artemisinin resistance includes significant progress in malaria surveillance in the artemisinin resistance response zones. However, in order to effectively respond to artemisinin resistance and to move towards malaria elimination, more detailed community level surveillance will be needed in remaining foci of transmission in order to guide local responses.

Figures 3 and 4 show that in both Cambodia and Thailand the annual peaks in transmission were reduced in 2010 and 2011 compared with 2009, following action in the containment zones .

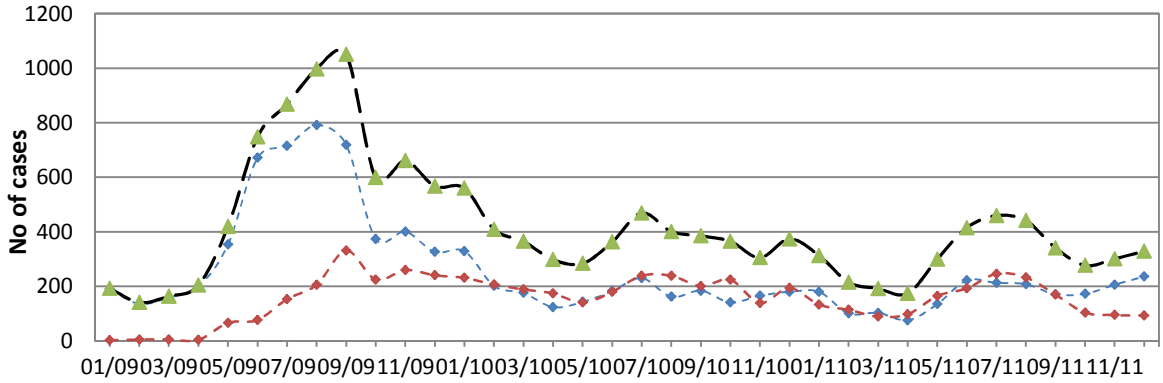
Figure 3. Malaria case numbers in containment zones* in Thailand



* "Zones" was the term used for what are refered to elsewhere in the text as "tiers". Pf = *P. falciparum,* Pv = *P. vivax*

Source: Thai Division of Vector Borne Diseases

Figure 4. Malaria Trends in Cambodia – July 2008-June 2011 in villages less than 10 km from border of Thailand *(Facilities in blue, Village Malaria Workers in red, all in green)*



Source: National Malaria Centre, Cambodia

Drug therapeutic efficacy surveillance has been able to detect the emergence of signs of artemisinin resistance across the GMS. This needs to be maintained in current sites to track changes but also to expand to new sites. Surveillance for parasitaemia on Day 3, the best proxy indicator for the potential emergence of resistance in an area, has been initiated in some areas. Experience to date has shown that it can be difficult to conduct with sufficient rigour to be useful in the remote areas of most

interest (see Box 2). Insecticide resistance surveillance has been given less attention, but is relevant, since vector control is an important tool in transmission reduction needed to eliminate resistant parasites. WHO and partners have established the Asia Pacific Insecticide Resistance Monitoring Network and are intensifying its implementation. Access to diagnosis and treatment in the public health sector has vastly increased due to the huge increase in availability of RDTs and artemisinin-based combination therapies (ACT) in all countries of the region. The use of village malaria volunteers to expand access has proven especially useful in Cambodia where they now detect and treat a significant proportion of cases. Most other GMS countries are also working with village volunteers in malaria control, offering the opportunity to involve them in response operations. In the private sector, however, a number of major issues persist.

Oral artemisinin monotherapy is still widely available, especially in Myanmar and China. Impressive results have been obtained in Cambodia and Thailand in reduction of this inappropriate treatment but much more needs to be done across the sub-region. Also, a large (though slowly decreasing) proportion of cases treated in the private sector do not receive prior diagnosis with microscopy or RDTs. Some experience has been gained, especially in Cambodia, Lao PDR and Myanmar, with public-private collaboration to improve the management of malaria in the private sector. Myanmar is embarking on an ambitious effort to replace monotherapy in the private sector with subsidized ACT. These experiences should be carefully evaluated.

To achieve elimination of resistant parasites it is essential to add a transmission-blocking drug to the treatment of *P. falciparum* malaria. Primaquine is the only available drug and its use is hampered by its potential side-effects in people with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Not much is known about the epidemiology of different variants of this condition in the GMS, nor the risk associated with them, and no field-ready test to screen for it currently exists. Therefore, although some countries have a policy of including primaquine in the standard treatment it is often not used. Resolution of questions around the safety of primaquine is urgently needed.

All countries are distributing long lasting insecticidal nets (LLINs) in artemisinin resistance response areas but in most the coverage is far from the universal coverage recommended for Tier 1 areas. Cambodia achieved a coverage of households with at least one insecticide treated net of 72% after mass distribution in 2009, but this fell to 63% by 2010. Migrants and mobile populations, who represent high risk groups, in particular, are not well covered. It was difficult in many cases to obtain accurate data on the coverage of key populations with LLINs, as some countries rely on data on what was distributed without validating coverage through household surveys. Indoor residual spraying (IRS) is also used, more often than not in response to outbreaks or foci of malaria, but strategies were not always clear. Very little is being tried with other personal protective measures, such as repellents, adapted, for example, for use by a number of different groups exposed by their occupation. In general, behaviour change communications/information, education, communications (BCC/IEC) is a relatively weak link in most response to artemisinin resistance efforts, though some innovative approaches have been tried on a small scale. The challenge now is to extend them to a larger scale.

The management of responses to artemisinin resistance relies heavily on the state of the national health systems, and strengthening these systems where needed is critical to maintaining adequate responses.

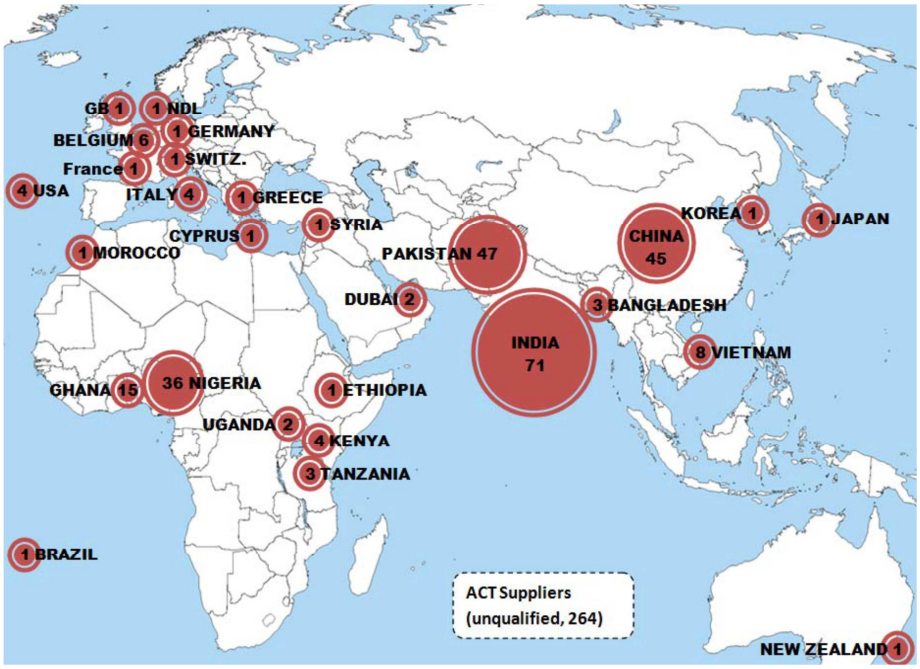
The role of WHO in supporting countries and in regional coordination is a critical one and needs to be further strengthened. Many other partners are involved in support to the response to artemisinin resistance at different levels, with significant funding coming from the GFATM and USAID across the sub-region and from BMGF, DFID and AusAID in Myanmar. With a proliferation of partners it has become challenging for NMCPs to coordinate action and in some countries there are no strong mechanisms for doing this. This is a priority and one in which WHO should provide stronger support to NMCPs.

3.4 Emerging challenges: funding, drug quality, targeting of research, political factors

The GFATM has been a major source of external funding for malaria control across the sub-region and in Cambodia and Thailand has awarded grants specifically focused on the response to artemisinin resistance. The financial crisis at the GFATM is already having a major impact. For example, Round 9, Phase 2, in Cambodia which is focused on the response to artemisinin resistance has been cut significantly; Round 10 in China has been suspended; and the postponement of Round 11 has cut off this channel of potential funding for the response to artemisinin resistance in Myanmar and Vietnam. Intensive efforts will be needed to increase domestic resources for the response to artemisinin resistance and identify regional and global funding.

The pharmaceutical sector can play a critical role in both preventing and encouraging resistance. Widespread export and sale of artemisinin monotherapies is a major concern. There are also concerns around the very large number of unqualified producers of ACTs - 264 - compared with the nine producers who are WHO pre-qualified (see Figure 5). This explains the concerns raised in the GMS about the very slow process of WHO prequalification for manufacturers of ACT, which leads to under exploitation of production capacity as well as providing an incentive to continue producing monotherapies. Tackling these issues will require action outside of the health sector at national and regional level and engagement with the pharmaceutical industry. Regional interest, for example in ASEAN for ensuring quality drug production and trade across the region and for rational drug use, including to slow the emergence of antimicrobial resistance, provide opportunities to address the issues around anti-malarial drugs.

Figure 5: Unqualified ACT Suppliers



Source: Roll Back Malaria Procurement and Supply Management Working Group Meeting, February 2012 - AEDES

This assessment gained an overview of research being undertaken, and associated gaps, in a number of areas of priority for improving the response to artemisinin resistance. Preventing the spread of artemisinin resistance with an effective transmission-blocking drug requires urgently determining a minimum safe and effective dose of primaquine (the only currently available option) and developing a test for G6PD deficiency to guide the use of primaquine. Other priorities include identifying molecular

markers for artemisinin resistance and understanding its mechanisms, improving *in vitro* drug susceptibility assays and developing highly sensitive diagnostics for malaria for use in low transmission areas. Improved preventive interventions, especially for mobile populations, is another key priority. The search for alternative drugs to ACTs is also critical. Better collaboration between NMCPs and research institutions would be mutually beneficial.

Political factors are an insufficiently considered dimension of artemisinin resistance development and the response to it at local, national and regional levels. These factors need to be taken into consideration in the implementation of the response to artemisinin resistance. They range from the political factors affecting the precarious status of high risk populations in some areas and the limitations on international support in Myanmar to the potential for regional bodies such as ASEAN and SAARC to play a role in mobilising political commitment to the response to artemisinin resistance. The potential for countries of the region to play a greater leadership role is also important to address.

While there is no evidence yet on artemisinin resistance beyond GMS, it is necessary to be proactive to prevent its emergence in, or spread to, other countries. Of particular importance are northeast India and the eastern part of Bangladesh where prevalence of *P. falciparum* is very high, population movement to and from Myanmar is heavy, and health service delivery is far from optimal. Also important is eastern Indonesia and Papua New Guinea where foci of intense transmission still occur, population movement is common, and oral artemisinin monotherapy is available.

4. Summary of achievements and enabling factors in the response to artemisinin resistance

Among the many **achievements** noted by this assessment are:

- In Cambodia and Thailand, which were the first countries to initiate programmes in response to artemisinin resistance, significant impact has been made on malaria in Containment Tiers 1 and 2.
- A GMS Therapeutic Efficacy Studies (TES) network that, with WHO coordination and technical support, has functioned over ten years and now includes sites in all six countries has been able to detect and map the presence of signs of artemisinin resistance. Out of almost 40 sites, about 20 are active each year.
- Malaria surveillance systems have significantly improved during the early responses to resistance of 2009 to 2011.
- Better access to diagnosis and treatment through community based agents has increased appropriate treatment.
- The numbers of insecticide treated nets delivered have increased in several of the countries, particularly in Tier 1 and 2 areas.
- The use of artemisinin monotherapy for uncomplicated malaria in the public sector has been virtually eliminated, although private sector use and export remain major issues.
- There has been greatly increased cross-border collaboration between governments and pragmatic cross-border approaches to uncontrolled border areas of Myanmar through NGOs.

Several important **enabling factors** have facilitated progress with the response to artemisinin resistance:

- There is a heightened awareness of artemisinin resistance and the potential risk that it poses to the very significant global investments that are being made in malaria control and elimination worldwide and to future success.
- GMS governments have been willing to collaborate in the response to artemisinin resistance.
- Until now there has been strong commitment of funding from some international donors and from the GFATM for the response to artemisinin resistance even though it is only one of many

pressing health development needs at a time when the global recession is having an impact on development budgets.

- Under the leadership of WHO countries of the GMS have made commitments to take action on artemisinin resistance. Four countries have elaborated national 'response to artemisinin resistance' strategies backed with some level (albeit incomplete) of cost assessment. China, though not having a response to artemisinin resistance strategy *per se,* is actively involved with relevant activities in its border areas in Yunnan Province.
- WHO's role in convening scientists, governments and development partners has contributed to a shared understanding of key issues.
- A research network is active across the GMS conducting studies to better understand the extent and mechanisms of artemisinin resistance and to improve the tools for tracking it.
- There is growing awareness of the need for regional action on ensuring access to quality medicines. This has potential implications in relation to standards for quality control of production and agreements governing trade.
- Recent political developments in Myanmar have allowed greater interaction with neighbouring countries and international organisations to the extent that a well-designed artemisinin resistance strategy, taking into account lessons from Thailand and Cambodia, has been endorsed.

5. Key issues identified

The main thrust of this assessment was to identify issues that could impede progress in the implementation of the response to artemisinin resistance and opportunities that could be exploited. This section of the report summarizes the issues identified.

5.1 Mechanisms for reaching consensus on policy issues

- **Mechanisms for supporting and monitoring implementation of recommendations agreed by countries need to be strengthened.** WHO has been active in convening expert meetings to address technical issues as they have arisen and in facilitating inter-country collaboration but these processes do not systematically lead to action.
- **Decisions on treatment regimens have mostly been taken nationally without regard for neighbouring country practices.** This has resulted in different treatments being used in adjacent areas within the same malaria transmission zone on different sides of borders.
- Assuming that the evolution of artemisinin resistance is not dependent on the actions of a single country **a more formal regional mechanism for reaching consensus appears necessary**. Even if decisions made would not be binding, at least consistent follow-up and peer pressure may result in compliance with consensus agreements.
- **Within countries, the process of moving from expert consensus to policy to implementation can also be slow.** This is not compatible with the urgency of the response to artemisinin resistance. Efficient facilitation of this process is needed.
- **Certain key issues that need to be addressed for an effective response to artemisinin resistance may be outside of the mandate of the Ministries of Health** and require a consensus mechanism that engages other government agencies across countries. Pertinent examples are the manufacture, private sector use and export of oral artesunate monotherapy, the issue of substandard and counterfeit antimalarial drugs and the treatment and control strategies employed by defence ministries.

5.2 Management of national response to artemisinin resistance operations

- **The command and management structure for the response to artemisinin resistance observed in most countries is not compatible with an urgent activity.** Often there is no person of adequate rank assigned as the full-time responsible officer for the response to artemisinin resistance. In some countries senior sub-national health authorities seem unaware of the importance of artemisinin resistance and their role in responding to it. Given the usually remote nature of artemisinin resistance areas categorised as Tiers I and II, effective daily (or weekly) management from the national (or in some cases even provincial) capital is difficult; continuous or frequent supportive supervision by health officers with authority is required.
- **Limited (real time) operations management data is available to assess the coverage, continuity and quality of key activities.** Monitoring systems are needed that allow supervisors to have immediate information on key operations such as case reporting, availability of RDTs and ACTs, LLIN distribution, IRS, special activities for high risk populations. Some progress has been made on this, but it is variable.
- **More rigorous and probing analysis of epidemiological trends and operational data is needed.** For example, dramatic long-term improvements in overall malaria incidence may mask more recent stagnation in malaria trends. Continuous performance assessment is needed both at the national and sub-national levels, linked to analysis and remedial action where required. Capacity for this seems to be limited outside of the NMCP core staff and premier institutions in most countries.
- **Commodity management is still a barrier to effective programme implementation.** All countries face chronic (or at least periodic) shortages of critical commodities such as LLINs, RDTs and ACTs. Distribution of available commodities is not necessarily well targeted to the populations or areas of greatest need e.g. in Tiers I. Procurement processes, including those of funding partners, often contribute to the delivery delays and stock-outs.
- **Weak health systems in some countries or areas represent a critical threat to mounting and maintaining an effective response to artemisinin resistance.** In particular, fluctuations in incentives to motivate health workers at all levels from national to community health worker level limit motivation and encourage diversion of effort to other priorities. Limited experience in coordination of public and private sector reduces the potential of private sector as a positive partner.
- **Major reforms of some NMCPs such as decentralization and integration, in some cases due to their successes, may constrain a focus on the response to artemisinin resistance efforts at least during the early stages of reform.** Parallel information systems and lack of necessary specialist skills and authority at local level where intensified intervention is needed for the response to artemisinin resistance are two particular risks. Well handled, however, they could provide opportunities to improve peripheral capacity and management of commodities and information.

5.3 Coordination of national and regional responses to artemisinin resistance operations

- **Mechanisms for coordination of multiple partners engaged in the response to artemisinin resistance are not sufficiently strong in some countries.** While most countries have a mechanism for coordination of malaria control activities, stakeholders tend to meet infrequently or only around specific technical themes or for major tasks (typically preparation of GFATM proposals where all stakeholders have a vested interest). Routine overall coordination of programme activities is much less common. Coordination of the response to artemisinin resistance activities is similarly deficient despite some countries having, on paper, a specific group for this. While WHO is always a partner in coordination meetings it needs to ensure that it consistently takes an active role in encouraging/supporting NMCPs to make them happen.

- **Within countries WHO has been unable to base staff in the field close to Tier 1 and 2 areas** as has been done in other similar programmes supported by WHO (e.g. smallpox eradication, polio elimination). This level of support is almost certainly required to achieve an effective response to artemisinin resistance.
- **WHO has the primary mandate for regional coordination and to support NMCPs in their interaction with other countries on programme implementation issues but is inadequately resourced to play this role.** Across countries WHO has convened many meetings and facilitated country collaboration. Resources to follow-up on recommendations emerging from these meetings by countries and partners (including WHO) has not always been adequate.
- **Although there seems to be a good division of labour and coordination of effort there is a need for absolute clarity of roles between WHO HQ, WPRO, SEARO and the bi-regional coordination office in Bangkok** that is understood by all stakeholders.
- **With more dedicated resources, WHO could more rapidly respond to emerging threats such as artemisinin resistance without waiting for external donor support.**
- **While WHO has the primary role for technical coordination other entities may be better placed to take the lead on securing high-level political support** (see below).
- **At present there is no mechanism involving major stakeholders for coordinating research related to artemisinin resistance in the GMS,** although a number of ad hoc meetings have been held with this purpose**.**
- **Non-governmental organizations (NGOs) play a valuable role but cannot coordinate governments nor work alongside governments to coordinate other partners in the same way that WHO can.** Their role is, however, critical and should be expanded, particularly in areas or activities in which NMCPs cannot provide adequate coverage. It would be helpful to define clearly the roles of all partners in the response to artemisinin resistance based on their strengths and mandates.

5.4 Political issues

- **Political awareness of artemisinin resistance is generally good, at least in the health sector**, in the countries visited by the joint assessment mission, but political **commitment** appears to be weaker, at least when measured by allocation of government resources.
- **There are challenges to keep artemisinin resistance on the domestic political agenda**. In countries that have greatly reduced malaria, artemisinin resistance can potentially be dismissed as "someone else's problem"; in those with a high malaria burden, artemisinin resistance may be perceived as just one of many important issues.
- **In contrast to artemisinin resistance, malaria elimination has political appeal and high level government support or endorsement**. So far all declarations of intent to eliminate malaria have been national, and with different target dates. The success of elimination efforts, as with the **success in controlling artemisinin resistance, will require an agreed upon regional effort, strongly coordinated, even though countries may have different timeframes.**
- **The emergence of artemisinin resistance coincides with multiple factors with strong political dimensions**: the global recession (and its impact on external funding for malaria control), a dynamic situation in relation to the regional power balance, increased population movement (including across borders), settlement or invasion of forest land for legal and illegal exploitation and acceleration of the decentralization of health systems and their financing.
- **Artemisinin resistance 'hotspots' are mostly at border areas, which inevitably have political complexities**, for example: international tensions played out in cross-border conflicts; relative autonomy (or neglect) from central authority; higher proportions of ethnic minorities that may be

seeking autonomy; corruption fueled by unregulated commercial exploitation of new territory. Cross border collaboration, even for relatively simple actions, may need to be sanctioned at central level and may thus be impeded by any bilateral tensions.

- **Malaria control in migrant and mobile populations is a challenge in all countries of the GMS and one with political dimensions.** Illegal (or undocumented) migrants are a case in point: they may avoid (and/or not have access to) official services, including for public health; they may be unregistered in commune/village records used for commodity distribution; and, despite a greater need in some cases, they may be given lower priority by public health measures. **These concerns also apply to internal migrants.**
- **Unilateral government actions to limit use/sale of artemisinin monotherapy or counterfeit or substandard antimalarial drugs will have limited impact on production and exports.** A regional agreement, rigorously followed-up, is needed (as is the case for counterfeits).
- **For the response to artemisinin resistance in the GMS to succeed some actions will need to be coordinated at global and regional levels through appropriate organizations.** The appropriate roles of different organizations need definition. In addition to a critical role for WHO, ASEAN, SAARC, APEC and other organizations can also contribute. The ASEAN+3 health ministers meeting in Thailand in July 2012 presents one specific opportunity.
- **China has the potential to play an influential role in the response to artemisinin resistance in the region**; this should be further explored. Chinese research and public health institutions, e.g. National Institute of Parasitic Diseases (NIPD) – China CDC and Yunnan Institute of Parasitic Diseases (YIPD), are willing to play a more regional capacity-building role but need WHO to coordinate inter-country collaboration. **China has one of the most important pharmaceutical industries in the region (along with India) with huge potential to influence the supply of ACTs and the non-supply of monotherapy.**
- **The warming relations between the West and Myanmar may bring opportunities to more effectively support the public sector**, but at the same time any influx of new partners and/or resources will also add to coordination and implementation challenges.
- **Increased technical and commercial interaction between Asia, particularly China, and Africa has implications for the spread of resistance.** Key areas to consider are the types and quality of malaria control commodities sold to Africa as part of growing business relations, the movement of potentially infected people from GMS countries to areas of high transmission in Africa leading to introduction of resistant parasites and the importance of open exchange of technical know-how and strategies.
- **An effective response to artemisinin resistance requires encouragement to health authorities at all levels to ensure that reporting of statistics is timely and accurate** and to report failure as well as success. Lessons learned are as important as good practices, and should be shared across countries.

5.5 Funding related issues

- **The overall funding gap for the response to artemisinin resistance in the GMS in the next five years is estimated to be at least $150 million.** WHO has worked with NMCPs in the GMS to estimate funding needs for malaria control/elimination and for the response to artemisinin resistance over the next five years, and to estimate the overall funding gap. To some extent separation of the needs for responding to artemisinin resistance from overall control/elimination requirements is arbitrary as the response to resistance needs to build on and be supported by ongoing general NMCP activities; the control/elimination activities also require additional funding. Consultation with the NMCPs provided an estimate of $35 million per year for operations in response to artemisinin resistance across the six countries. The GPARC estimates $ 10 million is

needed annually to cover regional/global activities and coordination. Both the GPARC and this joint assessment estimate $ 15 million is needed for research annually (excluding research for new non-artemisinin drug development). This gives a total need of $60 million per year of which it is estimated that around half may be available from existing sources of funding. This leaves a five-year funding gap of $150 million. The most significant gaps for country level operations are in Myanmar and Vietnam. The overall amount needed could be significantly higher if China considers that it needs to implement specific activities in response to artemisinin resistance or if there is more general geographic spread of resistance in the GMS.

- **Most national responses to artemisinin resistance are being run with very limited funding from domestic government budgets.** In some cases the overall national budget has decreased in recent years and as a consequence funding available for the response to artemisinin resistance has also decreased.
- **External funding across the GMS has also been inadequate to allow the intensification of activity needed for responding to artemisinin resistance**, with the exception of funding in Cambodia and Thailand during the now-ended ARCE Project. Although the GFATM and a small group of development partners have provided significant support, overall this has been inadequate. There is a need for a broader range of donors.
- **The impact of the GFATM financial crisis on the future response to artemisinin resistance is profound.** Myanmar and Vietnam are deprived of the possibility of applying for funding for the response to artemisinin resistance in Round 11 as had been planned and the Cambodia Round 9 funding which was specifically designed to continue ARCE Project activities is being cut by 35%. Termination of China's National Strategy Application funding will also have an impact.
- **The reliance of the GMS response to artemisinin resistance on external funding from different sources or projects has led to a high level of "projectization" of activities** in countries with significant external input (especially Cambodia and Myanmar) rather than integrated financing of a single national strategy and plan. This is inefficient and also considerably increases the coordination challenge for the NMCP. **A related issue is the lack of continuity that results when projects end.**
- **The implications of reductions or discontinuity in external funding go beyond just the decrease in financial resources.** External support for national institutions and NGOs can allow them to undertake activities across borders or in restricted areas, which it might otherwise be difficult to fund.
- **Supply of essential commodities has often been disrupted, at times for long periods.** One of the reasons frequently cited for this is the procurement procedures and rules (most frequently mentioned being those of the GFATM) that often put procurement principles above good public health, resulting in prolonged negotiations. Greater flexibility will be needed to ensure this situation does not persist.

5.6 Issues of diagnosis and treatment

- **Much of the strategy to respond to artemisinin resistance relies on non-artemisinin companion drugs in ACTs eliminating artemisinin resistant parasites. Therefore, increased treatment failure rates for dihydroartemisinin-piperaquine (DHA-PIP) in Western Cambodia and of artesunate-mefloquine in parts of Thailand are a major concern.** There are very few suitable companion drugs for artemisinins suitable for use in Southeast Asia, so efforts to preserve their efficacy are important. Use of piperaquine alone for prophylaxis, as observed in China, is inappropriate given its importance as a partner drug to artemisinins. Given the known presence of resistance to mefloquine a change of ACT is needed in Thailand. In countries where artesunate-mefloquine (AS-MEF) is still effective, the absence of a prequalified fixed dose AS-MEF formulation, or at least co-

packaging in blister packs, increases the risk of poor dosing with associated risks for development of resistance.

- **Use of a single transmission blocking dose of primaquine with ACT is important but constrained by concerns about safety in people with G6PD deficiency – an urgent research effort is needed to resolve key issues.** The priority is to evaluate the safety of the currently WHO-recommended single dose of 45 mg, and Thailand needs to determine whether its use of 30 mg is effective. Field tests and further development of simple point-of-care G6PD deficiency tests is also a high priority.
- **The widespread use of oral artemisinin derivative monotherapy (AMT) in the private sector and its continued unrestricted export from some manufacturing countries is detrimental to the response to artemisinin resistance.** Whilst some countries in the region have made excellent progress in controlling use of AMT (Thailand, China and Vietnam banned private sector sale of antimalarials, and in Cambodia and Lao PDR the enforcement of its AMT ban has been seen to bring down availability and frequency of use), the problem is still severe in Myanmar. Recent efforts to encourage the major supplier to switch to ACTs are a good start, but close monitoring and work with other potential suppliers should remain high on the agenda.
- **Use of ACTs without diagnosis confirmed by RDTs or microscopy is still common in some countries, and will unnecessarily contribute to drug pressure.** In Cambodia there is an encouraging progression in demand for or use of parasitological diagnosis before treatment, even in the private sector, but in Myanmar presumptive treatment is the norm in the private sector. The introduction of a policy of diagnosis before treatment is less challenging in the public sector than in the private sector, where new strategies are needed to incentivise private providers to confirm diagnosis (for example, to compensate them for treatments not sold).
- **Use of different treatment regimens in areas of similar malaria type/pattern across borders.** Whilst it is not essential for each country to use the same ACTs as first-line treatment, there are concerns in border areas with high population mobility. At the very least it is important to share information across border areas and for countries to consider changing treatment protocols if their neighbours detect treatment failures.
- **Reliability of supplies at all points of treatment is a fundamental requirement to limit resort to inappropriate alternatives.** Significant procurement issues related to the use of GFATM resources have hampered commodity supply. Cambodia has struggled, as there was not until very recently a prequalified supplier of DHA-PIP, whilst Vietnam, China and Thailand opted to use domestic resources to purchase their drugs of choice. The lack of prequalified DHA-PIP stalled its planned introduction through the Affordable Medicines Facility for Malaria (AMFm) for so long that the rationale for extensive supply to the private sector when incidence rates are declining needs to be reviewed. Myanmar has simply had inadequate funds to assure supplies.
- **Access to treatment by individuals at highest risk of contracting or spreading malaria is limited and needs better delivery systems.** Provision of services to mobile and migrant populations is a continuing and dynamic challenge. Not enough attention is yet given to the protection of migrant labourers. More substantial engagement with employers and business coalitions is needed. In addition, it appears that defence and police forces often lack resources to provide appropriate treatment for their staff. Myanmar has the added challenge of limited malaria treatment in areas outside of government control and access. Support for NGOs who may be able to work in such areas, whilst maintaining political neutrality, seems to be underexploited. In some countries of the GMS community-based **malaria workers have had great success in extending access to treatment; this approach should be considered in all countries.**
- **Quality of care in the private sector needs more attention.** Whilst some provision of diagnosis and treatment in the private sector is done well, and in several countries there is some crossover of those who work in both sectors, there is still a large unregulated provision of drugs and treatment of very poor quality in some areas. More understanding of how to work with the private sector and the appropriate level of investment in improving it is needed. There is debate

about whether sale of antimalarials should be banned altogether in the private sector, as has been done in Thailand and Vietnam. In countries where public sector reach is limited, however, lack of access to antimalarials in the private sector would lead to delays in necessary treatment.

5.7 Pharmaceutical sector-related issues

- **There is unused ACT production capacity in China while, globally, there is a problem with supply** (although there is some disagreement on the extent of the shortfall).
- **The WHO-led prequalification process is long and slow.** There are disincentives for participating, which may soon drive some potential manufacturers to abandon ACTs. Meanwhile production of monotherapy does not face these constraints. WHO and development partners need to expand sources of technical assistance for manufacturers wishing to achieve prequalification of their antimalarials.
- **Production, distribution and export of oral artemisinin-based monotherapies continue** from several countries (despite efforts to control domestic use, with some success in the public sector). Ministries of health often have limited influence over drug production. For example, in China the Ministry of Health is responsible for drug regulation for internal use while the Ministry of Commerce is responsible for quality control and regulation of drugs for export. According to the most recent WHO reports Myanmar is the only country in the region, which still allows marketing of oral artemisinin-based monotherapies (although it continues widely in some other countries). Myanmar plans not to renew current licences, which expire in 2012.
- **Counterfeit and sub-standard antimalarial drugs are still available** despite progress in this area. Recent surveys to detect substandard or counterfeit antimalarials in 2009-11 found substandard antimalarials in all four countries surveyed (Cambodia, Lao PDR, Thailand, Vietnam). There were more samples failing quality tests in Cambodia (12%) than in Thailand (1%).
- **Capacity to monitor for drug quality is limited.** The only results made available are those collected by external organisations. Local authorities may not share the data they collect as it may be sensitive. In addition there are challenges in determining sampling strategy and size needed to provide a sensitive surveillance system for substandard and counterfeit drugs.
- **There is still not enough activity to clamp down on production, distribution and export of counterfeit antimalarials.** There was considerable public debate on the issue a few years ago with involvement of WHO and Interpol, but there appears to be much less reporting more recently, and it is not clear what was achieved by earlier advocacy and investigation nor what more is needed.

5.8 Prevention-related issues

- **In all countries there is a shortage of LLINs relative to need, including in most Tier 1 and Tier 2 areas.** Coverage after mass distribution was estimated in Cambodia as 45% of households with one LLIN per two people and 59% with at least one LLIN. The supply of nets for migrants is, in all countries, a fraction of the need. In theory high ownership of LLINs is one of the most achievable objectives of the applied strategies, even if regular use may be more challenging to achieve. Compared with the complexity of several other interventions, provision of LLINs is relatively straightforward and should be prioritised.
- **Strategies to *maintain* high coverage of LLIN in at-risk groups are not clearly articulated and have not been tested in several countries.** Reasons for fall-off in coverage after special LLIN distribution campaigns need attention to ensure everyone who needs a net has one continuously. A mixed model system of free LLINs provided through routine systems, regular access to special distributions if needed, and improved commercial sector availability should enable continuous

access and take advantage of a strong culture of net purchase. High-risk mobile and migrant populations need to be targeted with appropriate health promotion activities.

- **Little effort (including in research) has to-date been invested in alternative approaches to personal protection, especially for population groups who due to occupation or lifestyle would be poorly protected by LLINs.** These include workers (often migrants) who sleep outside in the forest or engage in outdoor work during *Anopheles* biting hours such as rubber tappers. Where hammocks are used for outdoor sleeping long-lasting insecticide treated hammock nets can provide protection. Migrant workers can be lent bednets by their employers. Repellents could be more widely used for certain groups. To use resources efficiently strategies to protect high-risk groups should be linked to good epidemiological studies, such as those identifying potential "super-spreaders" in Myanmar.
- **There is a huge (and welcome) private sector market for mosquito nets in countries of GMS, but only a small fraction of the commercial market is for LLINs.** Sustainable and affordable strategies to move from untreated nets to LLINs in the private sector are urgently needed, and require dialogue with importers and manufacturers. Interim strategies such as bundling insecticide with nets for commercial sale (as currently piloted in Cambodia) are potentially important but costly. A deeper understanding of market forces, price sensitivity, potential for technology transfer and customer choice is needed as part of a strategy review across the region. Some of this work has recently begun.
- **The response to detection of foci of cases around Day 3 parasitaemia or treatment failure index needs more evidence.** Countries have adopted different approaches to case investigation either investigating all malaria cases in areas of very low transmission or investigation of origins of "resistant" cases. Associated responses include top-up provision of LLINs, indoor residual spraying, screening and treatment and BCC/IEC. These may cover in a specified number of houses or radius from the home of the index case. It is difficult to find data on the implementation rates of these responses. Further, the optimal response to achieve the goal of elimination of all resistant parasites is unevaluated and unknown. While it is reasonable to begin with a pragmatic approach involving some assumptions and an assessment of feasibility and cost, it is also important to obtain better evidence. Such research would also be relevant for malaria elimination more generally.

5.9 Surveillance issues

- **In all countries reporting of cases from the private sector is limited.** In Cambodia, where approximately 60% of treatments are obtained in the private sector, a number of initiatives have been tried in the past ten years to incentivise private sector reporting, but the sustainability of such initiatives beyond externally-supported pilots is limited. There could be scope to improve malaria surveillance among private providers and other networks (such as farm owners and border patrols) using SMS. The need to improve reporting was more recently mentioned in Cambodia's public-private partnership strategy. The critical question to address is how important is such information and at what stage is it most needed.
- **The high proportion of cases detected by Volunteer Malaria Workers in Cambodia is an impressive indication of extended access to treatment.** It will be important to maintain good supervision of VMWs and other community level agents to ensure that the data are accurate.
- **Excellent progress has been made in developing systems for capturing real-time data, but there is limited capacity to respond to local surveillance data.** There are several priorities in relation to this issue. The first is to be clear what information needs an immediate response. The second is to test the feasibility and impact of potential responses. The third is to ensure the data are available and understood by those responsible for using them.

- **Appropriate responses to detection of Day 3 parasitaemia from hospital and community-based surveillance need to be evaluated and implemented.** Similarly, clear thresholds are needed for reporting of individual *P. falciparum* cases (when first detected). Where large numbers of cases continue to be reported from particular villages, responding to individual cases is not appropriate.
- **All countries in the region have approaches to the stratification of districts or villages by risk of malaria, but the accuracy may be limited by changes in population and environment.** With rapid changes in forest cover and population movements, previous criteria for stratification have become less useful. Some of the criteria are based on vector presence or absence, yet there is little evidence that regular entomological surveillance takes place. Criteria for stratification need review, and there is a need to move to using village level data for stratification. Cambodia, Lao PDR and Vietnam have made good progress on doing this, and Myanmar is just beginning, but needs further support.
- **Artemisinin resistance is a regional problem and data sharing among countries is important.** During the time of the BMGF funding of the ARCE project in Thailand and Cambodia, there were regular fora for information sharing. It will be important for countries to continue to share data on a regular basis, but this is likely to need external support.
- **Several countries have developed malaria-specific case reporting systems.** Given weaknesses in timeliness and completeness of general health information systems there is some justification for setting up parallel systems to deal with potential emergencies such as the spread of artemisinin resistance, but there are strong arguments to work harder on harmonising systems to avoid wasting resources.
- **It is of critical importance to maintain, and where necessary scale-up the GMS therapeutic efficacy surveillance (TES) network.** As TES is a standard procedure for monitoring antimalarial resistance, GMS countries should be encouraged to finance it as a part of the core malaria programme (reducing dependence on external funding). Strong coordination and technical support through WHO is essential to the sustainability of the network, and helps to ensure application of WHO standards, appropriate and consistent data analysis and interpretation, timely advice to national drug policy decision-makers, and sharing of data and experience with neighbouring countries.
- **Roll-out of Day 3 parasitaemia surveillance and interpretation of the data generated should be undertaken with caution and conducted according to WHO guidelines.** Day 3 parasitaemia data are useful to supplement, not to replace, TES data. Parasite clearance is a function of multiple factors including the parasite, drug and host characteristics. Day 3 parasitaemia is believed to be an early sign of reduced artemisinin activity but has not been shown to be associated with ACT treatment outcomes. Successful implementation of Day 3 parasitaemia surveillance requires more investment in system scale-up and strategic planning. In order for Day 3 parasitaemia data to be interpretable, data collection must be coupled with DOT and quality controlled standardized microscopy; both are difficult in remote settings.

5.10 Monitoring and Evaluation (M&E)

- **In addition to managing a response to artemisinin resistance countries have national control or elimination strategies, multiple GFATM grants and other externally funded activities leading to too many demands for separate data.** Good efforts have been made towards supporting each country to develop its own national malaria monitoring and evaluation framework, but there are still pressures to adapt indicators to meet the needs of external agencies or regional and global plans. Work on harmonising monitoring and evaluation plans and indicators needs to continue. A bi-regional monitoring and evaluation framework has been developed sponsored by USAID, suggesting standardised indicators for countries to consider.

- **With multiple partners reporting to multiple donors as well as multiple research projects, it becomes important to make the best use of surveys to ensure comprehensive, timely but only necessary data are collected.** Household surveys are essential to measure both malariometric indices but also coverage and quality of interventions. Several key indicators can only be measured this way, but careful consideration is needed on the frequency of surveys and the number of questions. There should be a common survey protocol used across GMS. Efforts to share experiences among countries are important.
- **More in-depth evaluation of focal screening and treatment (FSAT) and possibly highly focal mass drug administration (MDA), and other intensified responses including vector control and BCC approaches is needed.** Practical experience in managing strategies to respond to artemisinin resistance is still very limited and extensive monitoring and evaluation is critical to refine strategies and assess impact of specific measures. Selection of suitable impact indicators was the most difficult and contentious area in the early phase of the response to artemisinin resistance, and there is still a challenge to interpret changes in Day 3 positive rates. Although achievements in measuring reduction in malaria and progress towards elimination of *P. falciparum* are easier and highly relevant, it is important to remember that the areas with the highest resistance are not the areas of highest prevalence.

5.11 Research

- **The GMS lacks a clear strategy on the addition of primaquine to ACT for treatment of *P. falciparum* malaria including how to reduce the risk of adverse effects to an acceptable minimal level.** Research is needed to determine the minimum safe and effective dose. This could start with assessing the safety of a single 45 mg dose as recommended by WHO. Given the costs of clinical research the possibility of combining research on use of primaquine in *P. vivax* and *P. falciparum* should be explored. Where trials of primaquine safety are needed, a multi-centre effort using a common protocol could accelerate the process and save money.
- **Closely linked to this is the need for an affordable, rapid and field-ready test for G6PD deficiency and a better understanding of the epidemiology of the condition, including in the multiple ethnic minority groups in malarious areas of the GMS.** Common research protocols and survey instruments could be used to allow comparison of new tests across different populations/settings. It is important to recognize that population survey G6PD deficiency data, while useful for understanding the epidemiology and genetic mapping of G6PD deficiency, will not fully replace the need to screen individuals prior to primaquine therapy.
- **A high priority for research in support of the response to artemisinin resistance in the GMS is to continue the search for a molecular marker of artemisinin resistance and for a better understanding of its resistance mechanisms,** in order to rapidly detect its presence and track its spread. Given the large sample sizes needed for such studies it is essential that NMCPs and research institutes collaborate across the GMS to ensure this research progresses as rapidly as possible without gaps in continuity of funding after next year.
- **While insecticide resistance monitoring has been scaled up in the GMS, research on personal protective measures has been only sparsely conducted.** Given the known limitations of LLINs for protecting the large numbers of people who are exposed to malaria in the GMS by the nature of their occupation or living habits, this is a high priority. Good research data on the effectiveness and acceptability of insecticide-impregnated clothes, repellents and other measures in different communities are still lacking. Research to control outdoor transmission should be given priority.
- **There is a need to review the organization and financing of *in vitro* drug susceptibility monitoring to ensure optimal use of limited resources, and to continue research to identify reliable assays for artemisinin resistance.** Although no reliable assay methods have been established for artemisinins, *in vitro* susceptibility monitoring of ACT partner drugs and conventional anti-malarials

remains useful and, where capability exists, the monitoring should be maintained. Given the necessary technical capability and costs of maintaining capacity in this area it would be beneficial if NMCPs would collaborate with local research institutes so that *in vitro* assay data can be generated and shared in parallel to *in vivo* or TES monitoring. Efforts to modify *in vitro* assays to reliably measure artemisinin resistance need to be further supported. New, non-isotopic *in vitro* drug susceptibility assay methods should be field-evaluated. However, given the challenges of sustaining *in vitro* testing capacity, it may be a higher priority to strengthen capacity for molecular marker and pharmacokinetic studies.

- **Effective response to artemisinin resistance (and malaria elimination) will require highly sensitive diagnostic tools for low-density parasitaemia that as yet do not exist.** The ability to detect every malaria case, including those that would be missed by field microscopy or RDT, has become more urgent. There are several polymerase chain reaction (PCR)-based methods in the pipeline that have yet to be fully validated for accuracy and feasibility under field conditions. These tests have not received priority consideration in the past and their development, especially those suitable for high throughputs, has been slow.
- **Not enough is known about the patterns of movement, living, employment and health care seeking behaviour of migrants and mobile populations across the GMS** despite their potential importance to the emergence and spread of artemisinin resistance. Better research methods are needed for studying these factors and the malaria exposure risks of populations involved in different occupations such as logging, gold mining, rubber plantations and different types of agricultural work. Options for malaria prevention (including transit and workplace approaches) and models of health care provision for these populations need to be explored.
- **Very few new drugs are in the research and development pipeline that could replace ACT in the event that artemisinin resistance becomes significant. It is urgent to expand research in this area.** The newly approved, artesunate-pyronaridine (Pyramax®) being itself an ACT is not considered ideal as a replacement for currently used ACTs. Malarone, a non-ACT being used in areas of decreased response to ACT in the border between Thailand and Cambodia area, is not intended for a long-term use, as it is prone to resistance development. Only a few synthetic artemisinins and non-artemisinins are in the pipeline as potential alternatives to ACTs.

5.12 Communications, advocacy and documentation

- **As part of the initial phase of the response to artemisinin resistance, a communications and advocacy strategy was developed and implemented, including events, literature, films, websites and meetings, but there was considerable lack of global awareness of what was being done.** Whilst the advocacy and communications activities did need considerable resources, and developed some very effective messages which gradually garnered greater support from donors, there is a risk of losing momentum as the story becomes old news. There is also a need to enhance the impact of local advocacy to expand political interest at local government level.
- **Numerous publications have been produced from some areas of the response to artemisinin resistance, but less is being published from other parts.** Whilst there is a wealth of material both published and unpublished, it will be important to make sure the information does reach the people who can make most use of it, and that repositories of information are accessible to each country. It is particularly important that research data are made available to implementers in a timely manner, even before publication.

5.13 Behaviour Change Communication/ Information Education Communication (BCC/IEC)

- **The strong emphasis on joint strategy development and joint messaging and bilingual materials development between Thailand and Cambodia has not been replicated among other**

neighbouring countries in the region. The process of working across the border was central to early response activities, and could provide lessons for other border areas.

- **Innovative approaches to BCC, such as positive deviance approaches, have been implemented but not fully evaluated.** More extensive evaluation of BCC/IEC strategies and activities will be important to refine strategies throughout the region. A challenge has been to identify meaningful and measureable indicators of behaviour and knowledge change. Household surveys have provided useful data on trends in some of the countries, but more understanding of reach of information to, and influence of communication on, key mobile and migrant target groups will be important.
- **The extent to which key groups (such as farm or plantation owners, development project managers and defence force leaders) are being targeted with effective BCC/IEC is unclear.** These are important target audiences and need to be reached.
- **Social scientists and communications specialists should be involved in development and implementation of BCC strategies. The strategies should be evidence-based.** Use of pamphlets and billboards, for example, has been shown to be of limited value, especially for semi-literate populations.

Conclusion

The extensive discussion above of issues to be considered in taking forward a strategy with a real chance to avert one of the greatest threats so far to progress in the fight against malaria, needs to be followed up by careful thinking and dialogue among stakeholders at all levels. The strategy needs to ensure momentum is maintained but without wasting increasingly scarce resources on approaches that lack evidence or are poorly managed. This can be achieved by harmonisation of efforts and of contributions from all stakeholders. The lessons learned will have added benefits in setting up the systems and capacity for malaria elimination. Without commitment to tackling the problem urgently, the costs – in terms of lives and money – are likely to be great.