Synthesis of the Current Evidence on the Multiple Causes of Malaria Drug Resistance

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### Acronyms

<table>
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<tr>
<th>Acronym</th>
<th>Description</th>
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<tr>
<td>ACT</td>
<td>Artemisinin-based combination therapy</td>
</tr>
<tr>
<td>ALM</td>
<td>ASEAN Labour Ministers</td>
</tr>
<tr>
<td>APLMA</td>
<td>Asia Pacific Leaders Malaria Alliance</td>
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<tr>
<td>AQMTF</td>
<td>Access to Quality Medicine and Other Technology Task Force</td>
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<tr>
<td>AR</td>
<td>Artemisin resistance</td>
</tr>
<tr>
<td>ASEAN</td>
<td>Association of Southeast Asian Nations</td>
</tr>
<tr>
<td>ERAR</td>
<td>Emergency Response to artesinin resistance</td>
</tr>
<tr>
<td>G6PD</td>
<td>Glucose-6-Phosphate Dehydrogenase</td>
</tr>
<tr>
<td>GMS</td>
<td>Greater Mekong Subregion</td>
</tr>
<tr>
<td>K13</td>
<td>Kelch 13</td>
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<tr>
<td>P. falciparum</td>
<td>Plasmodium falciparum</td>
</tr>
<tr>
<td>RDT</td>
<td>Rapid Diagnostic Test</td>
</tr>
<tr>
<td>SP</td>
<td>Sulfadoxine-Pyrimethamine</td>
</tr>
<tr>
<td>TES</td>
<td>Therapeutic Efficacy Studies</td>
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<td>WHO</td>
<td>World Health Organisation</td>
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Executive summary

This paper - focused on the current evidence on the multiple causes of malaria drug resistance - has been commissioned for the second meeting of the Access to Quality Medicine and Other Technology Task Force (AQMTF) in June 2014. The paper gives an overview of the theory and evidence on the potential causes of artemisinin and artemisinin-based combination therapy (ACT) drug resistance as well as a description of the factors that accelerate its spread. The paper suggests policy options for national, industry and regional action to better manage drug efficacy and reduce the emergence and spread of resistance.

Key messages

Artemisinin resistance is an extraordinary event that is expanding geographically within the Greater Mekong Subregion (GMS). As such, artemisinin resistance constitutes a major public health risk, within countries where it has been detected, and to other countries both in the region and globally. Artemisinin resistance requires a coordinated regional and international response. The situation is worsening and there is a need to act more aggressively and with more agility to get ahead of an evolving problem.

The emergence of artemisinin resistance is complex. However some sound theories have been developed as to its potential causes. Key factors, within the control of malaria programs, are overtreatment of fever cases and/or under-treatment of confirmed malaria cases.

For a malaria patient to receive the correct treatment certain conditions need to be in place including: the availability of high-quality antimalarials at the correct concentrations to kill parasites; the absence of sub-standard drugs and monotherapies; adequate knowledge amongst health workers of the correct management of malaria; the availability of high-quality diagnostics; easy and affordable access to health care; and adequate patient compliance with treatment.

Confirmed diagnosis of malaria is especially important in low transmission areas to prevent overtreatment of the disease, treatment of non-malarial fevers with antimalarials and ‘drug pressure’. Having a large proportion of people with variable concentrations of antimalarial drug in their bloodstream could lead to ‘selection’ for drug resistant forms of the parasite. Overtreatment could

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1 GMS Countries: Cambodia, the People’s Republic of China (specifically Yunnan Province and Guangxi Zhuang Autonomous Region, Lao People’s Democratic Republic, Myanmar, Thailand and Vietnam.
happen either when health workers treat without testing, or when people ill with malaria treat themselves.

Under-treatment can occur when antimalarials contain sub-therapeutic amounts of the active ingredient or when partial or incomplete treatments are taken for reasons of provider or patient behaviour. Under-treatment could increase the risk of the ‘selection’ and subsequent spread of drug-resistant parasites. For combination therapies, poor-quality of either one of the drugs effectively reduces treatment to a monotherapy, which could lead to an increase in resistance.

Artemisinin monotherapy directly selects for artemisinin resistant parasites. This type of therapy needs to be eliminated immediately.

We have a new and potentially powerful tool to detect and monitor the spread of artemisinin resistance. In 2013, a mutant protein in the *Plasmodium falciparum* (*P. falciparum*) parasite, Kelch 13 (K13), was identified as a molecular marker associated with delayed parasite clearance in patients treated with artemisinin. With the identification of K13, studies have begun to evaluate the presence of this marker throughout the region. In Cambodia, K13 mutants have been predominantly been found in the western part of the country with fewer found in the central and eastern areas. Emergence of artemisinin resistance in southern Laos has been confirmed using the marker. In Myanmar studies to evaluate the presence of K13 mutants are ongoing.

The most recent evidence indicates that artemisinin drug resistance has emerged independently in multiple sites in the GMS. In Africa, to date, there are no reports of delayed parasite clearance, nor has there been the identification of any molecular markers for artemisinin resistance. However, it is likely that artemisinin resistance will follow a similar pattern to chloroquine resistance in the 1950s; emerging in the GMS, spreading through Myanmar, across India to east and then west Africa. It has the same potential to have devastating effects on malaria control efforts worldwide.

High levels of cross-border and internal migration in the GMS region necessitates malaria control and elimination strategies that give attention to transborder coordination, rather than focussing solely on national aims. This requires strong multisectoral, cross-border collaboration between countries in the region. There is a need to reach beyond health programs to eliminate *P. falciparum* and artemisinin resistance.

Given the regional nature of the threat, countries have a vested interest in ensuring that their neighbours are rapidly detecting and responding to artemisinin resistance. As such, countries should be able to hold each other accountable for their progress in the detection and elimination of artemisinin
resistance. Monitoring of progress needs to be done by an objective and responsive body such as an independent monitoring committee.

**Regional Policy Options to support national implementation**

The emergence of artemisinin resistance in the GMS is of grave concern especially given early indications of its likelihood to spread beyond current areas and across international borders. Given the real and imminent threat posed by artemisinin resistance to the GMS, Asia Pacific and other regions, the following are recommended as policy options:

**Member states of the Asia Pacific region formally advocate World Health Organisation (WHO) for artemisinin resistance to be declared a Public Health Emergency of International Concern.**

If artemisinin resistance spreads, it may no longer be possible to reduce malaria transmission or effectively treat malaria cases. Malaria cases, both uncomplicated and severe, would increase significantly and rates of mortality could return to the same or greater than seen pre-2000.25 As a result, global malaria mortality could increase by 25 per cent. Given this potential impact of artemisinin resistance, it is imperative that countries within the GMS and beyond urgently advocate for a review of the artemisinin resistance situation and declaration of it as a Public Health Emergency of International Concern.

Following is a list of possible policy options for consideration by public health leaders in the region and by the International Health Regulations Emergency Review Committee.

**Strengthen cross-border collaboration for surveillance of artemisinin resistance.**

The detection and delineation of the artemisinin resistance problem is key to how responses are shaped. Surveillance needs to be prioritised as does information sharing across borders. Activities that are already underway, for example testing for the K13 molecular marker and Therapeutic Efficacy Studies need to be supported and enhanced where necessary.

**Ensure adequate supply of quality diagnostics and therapies to meet regional needs.**

A secure supply of high quality efficacious artemisinin-based combination therapy (ACTs) and Rapid Diagnostic Tests (RDTs) in the region relies on strong collaboration with the pharmaceutical sector from planning for new antimalarials, forecasting needs, through to quality assurance at point of care. ACTs are the last line of antimalarials and as such there is an urgent need to develop alternatives, or ideally a malaria vaccine. Regional collaboration with the pharmaceutical sector on research and development is essential. In addition, Asia Pacific Leaders Malaria Alliance (APLMA) could promote regional
manufacturers to be supported to go through the WHO prequalification process. Ensuring good manufacturing practices in the region should, in theory, lead to the replacement of substandard ACTs with high-quality products of increased affordability due to increased competition.

**Strengthen national regulatory capacity and enforcement to ensure quality of antimalarial drugs and diagnostics.**

Fake drugs kill, and monotherapies or substandard drugs could accelerate the emergence of artemisinin resistance. Halting the manufacture, distribution and use of oral artemisinin monotherapies and the removal of fake and substandard medicines from the region are high priorities. Only limited resources exist regionally to measure the quality of RDTs. It would be useful to have adequate continuous regional capacity to assure the quality of RDTs and future diagnostic products.

**Develop and implement a program of prequalification of primaquine products and ensure registration of their use in countries as a single 15mg dose for prevention of transmission.**

Adding primaquine to ACTs could help to slow the emergence of artemisinin resistance. However before this is possible, a number of constraints need to be addressed. These include: primaquine’s registration status; a limited numbers of pre-qualified manufacturers; and lack of designated regional laboratories for quality control.

**Increase regional collaboration for a more agile and aggressive response to artemisinin resistance.**

In addition to intensification of standard control measures, **extraordinary** measures should be considered in “hotspots” of artemisinin resistance, including those where the K13 molecular marker has been identified. Regional agreements could be developed around how to identify and actively respond to artemisinin resistant hotspots and surrounding areas as they emerge. These and other urgent measures need to be supported by a rapid response taskforce with capability to provide support to national teams where hotspots have been identified.

**Answer priority local research questions urgently, as they arise.**

There is an immediate need for a small but highly flexible funding mechanism for rapid grants to research on urgent operational bottlenecks, e.g. alternative ACT dosage regimens.

**Strengthen cross-border and multisectoral collaboration in priority areas.**

Effective and sustainable elimination of *P. falciparum* malaria, and specifically artemisinin resistance, requires concerted coordinated efforts of multiple sectors (See Annex 1), globally, regionally and across inter- and intra-national boundaries. Existing regional initiatives, for example Association of Southeast
Asian Nations (ASEAN or ASEAN+), could be mapped, built upon and more adequately financed if necessary. Where multi-sectoral cross-border mechanisms are not in place, short, time-limited high-level taskforces could be created to address specific issues relevant to artemisinin resistance.

**Track and respond to progress on artemisinin resistance continuously.**

APLMA as a regional collaboration mechanism, and by mutual consent among its members, could help to hold countries accountable for their progress in the implementation of commonly agreed measures for the detection and elimination of artemisinin resistance. To ensure objectivity and responsiveness, verification of progress could be done by an independent group such as the Independent Monitoring and Support Group proposed under the Global Fund’s Regional Artemisinin Initiative.
1. Introduction

This paper - focused on the current evidence on the multiple causes of malaria drug resistance - has been commissioned for the second meeting of the Access to Quality Medicine and Other Technology Task Force (AQMTF) in June 2014. The objective of this paper is to provide an overview of the evidence on the causes of artemisinin and artemisinin-based combination therapy (ACT) drug resistance as well as a description of the factors that accelerate its spread. The paper suggests policy options for national, industry and regional action to better manage drug efficacy and reduce the emergence and spread of resistance. It also provides an update of the latest known incidence of artemisinin resistance (AR) and AR molecular markers.

As background to the understanding of AR and its causes, Box 1 provides a simple overview of the theory of how malaria parasites develop resistance to antimalarial drugs. Section 2 of the paper focuses on ACTs, how resistance to artemisinin has been detected and current evidence of its geographical extension. Section 3 summarizes health system and social factors that may favour or accelerate the occurrence of AR. The final section explores the progress that has been made to date on addressing artemisinin and ACT resistance and suggests possible policy options for consideration by public health leaders in the region.

Evidence has been collated through literature and document reviews, coordination with key World Health Organisation (WHO) technical personnel and key informant interviews with experts in the field of antimalarial and artemisinin drug resistance. Key technical documents that were drawn on for the review are listed at the end of this paper. Articles and documents have been translated into less technical terms for our purposes.

Key informants included Dr Pascal Ringwald (WHO), Dr Nick White (Mahidol Oxford Research Unit), Dr Cally Roper (London School of Hygiene and Tropical Medicine), Dr Sylvia Meek (Malaria Consortium) and Professor David Heymann (Head of Global Health Security, Chatham House).
Box 1: How do malaria parasites develop resistance to antimalarial drugs?

For a malaria parasite to survive in its human host it must: compete with other parasite strains, evade the host’s immune defences and resist being killed by antimalarials. In high malaria transmission areas, the parasite faces all three of these challenges. In lower transmission areas there are generally fewer strains of the parasite to compete with and people also have lower immunity, so the parasite’s major challenge is surviving antimalarial treatment. Antimalarials kill parasites that are ‘susceptible’ or ‘sensitive’. But when any organism reproduces, random genetic mutations can occur, and a susceptible parasite may acquire a mutation that provides protection from an antimalarial. Malaria parasites can reproduce rapidly, with up to a trillion parasites in a severely ill patient, so it is likely that a few parasites will have protective mutations. Their survival largely depends upon whether the infected person has some immunity to eliminate them or becomes ill and seeks treatment.

When someone with low immunity becomes infected high parasite densities may occur in the blood and liver making them more likely to become ill and seek treatment. Where some parasites have mutated to become partially or fully resistant to antimalarials, treatment could result in the elimination of susceptible parasites leaving the resistant parasite population with no competition. ‘Drug selection’ has occurred, meaning that the treatment has killed the susceptible parasites and ‘selected for’ any resistant strains with mutations that confer protection. In theory, if a resistant malaria parasite is transmitted to a new human host who has low concentrations of antimalarials in their bloodstream, the resistant parasite has an advantage over susceptible parasites in the same host. Without any antimalarial in the new host, a susceptible parasite could outcompete its resistant cousin. Researchers think that resistance to antimalarials often comes at a cost (a ‘fitness cost’), for example slowing the parasite’s ability to digest or quickly reproduce. This makes a resistant parasite less able to compete with susceptible parasites in a human host in the absence of the antimalarial to which it is resistant. The advantage for a resistant parasite in a human population, therefore, depends on the proportion of infections that are treated. Increased drug use within a population is thought to lead to a greater probability of selection for resistant mutants.1

Evidence to date suggests that a malaria parasite does not develop complete resistance to antimalarials with just one mutation. Antimalarials may target multiple sites within the parasite, but initially mutations within the parasite may only protect one or two of the sites under attack making it partially resistant. With time, and additional exposure to the same drug, the parasite could accumulate a variety of mutations to gradually become fully resistant to the antimalarial even at higher concentrations.
2. Artemisinin Combination Therapy and drug resistance

ACT is the first line treatment option for *Plasmodium falciparum* (*P. falciparum*) malaria in all malaria endemic countries (and in some is also recommended treatment for other malaria species). Since 2000, malaria endemic countries have confirmed resistance to all other first line therapies and replaced those with ACTs. ACTs are the best, but the last, line of existing antimalarials suitable for wide-scale use for malaria control and elimination. Drug development for alternative therapies has been slow and new drugs are not likely to be ready for wide use until perhaps 10 years from now.

2.1 How does ACT work?

The mode of action of antimalarials is not fully understood, but most are thought to kill parasites either by disrupting their metabolic processes or preventing the parasite from reproducing. While the mode of action of artemisinin is not completely clear, recent evidence shows that artemisinin derivatives kill the parasite by disrupting its calcium pump, which is vital for cellular processes.5

Artemisinin drugs have very short half-lives (a measure of the amount of time they remain effective in a patient’s bloodstream after treatment); their concentration in the blood decays within a few hours. Other drugs have much longer half-lives, for example, lumefantrine (five days) or piperaquine (five weeks).

Combination therapies aim to combine drugs that attack multiple sites and life-stages of the parasite simultaneously. By doing this, the risk of resistance developing to either of the drugs is reduced. ACT combines a fast-acting artemisinin drug with a “partner drug” that has a longer half-life. After most of the parasites are killed by the fast acting artemisinin, the longer acting drug has time to ‘mop up’ any remaining parasite in the patient’s bloodstream and liver. In theory, a parasite that is resistant to one of the drugs will not be resistant to the other.

Current WHO treatment guidelines recommend use of ACT for three days. The relatively short treatment time is designed to improve patient adherence to the drug as a longer but more effective course (e.g. seven days) would be difficult. However, a consequence of the ACT design and regimen is that partner drugs act as a monotherapy.7 This means that more parasites are exposed to the partner medicine acting alone, increasing the risk of it developing resistance and the likelihood of treatment failures. Most patients with delayed response to artemisinin are cured provided that the partner drug remains effective.8 It is clear that the selection of partner drugs for ACT formulation, and monitoring of resistance to them, are critical.
2.2 How has resistance to Artemisinin Combination Therapy been detected?

Monitoring the efficacy of antimalarial medicines is a key component of malaria control and essential in the face of AR. Efficacy is mainly measured through Therapeutic Efficacy Studies (TES), which are in vivo evaluations of patients’ clinical and parasitological responses to directly observed treatment for uncomplicated malaria. Normally, therapeutic outcomes are assessed on the final day of the study (day 28, or day 42 for drugs with longer half-lives). TES form part of a global surveillance system to monitor the emergence of antimalarial drug resistance.

**Current WHO definition of artemisinin resistance**

The working definition of AR is based on observations from routine TES of ACTs and clinical trials of artemisinin monotherapy:

- **Suspected resistance:** an increase in parasite clearance time, as evidenced by ≥ 10 per cent of cases with parasites detectable on a three day treatment within an ACT (suspected resistance); or

- **Confirmed resistance:** treatment failure after treatment with an oral artemisinin-based monotherapy with adequate antimalarial blood concentration, as evidenced by the persistence of parasites for seven days, or the presence of parasites at day three and recrudescence within 28/42 days.

The definition of delayed parasite clearance has not been agreed, but, in general, AR is associated with a delayed parasite clearance rate double that of drug-susceptible infections.⁹

An increase in parasite clearance time (or delayed parasite clearance) is not a treatment failure and will not necessarily lead to treatment failure. In the Greater Mekong Subregion (GMS), treatment failure following treatment with an ACT has only been observed where resistance to the partner drug exists regardless of the presence of delayed parasite clearance for artemisinin.⁸ If the proportion of patients with a treatment failure exceeds 10 per cent a change in the national treatment policy should be made.⁸

Antimalarial resistance can also be measured using in vitro molecular studies that examine whether a parasite has genetic mutations associated with antimalarial drug resistance. Mutations associated with resistance to an antimalarial are referred to as molecular markers. As parasites develop resistance in different ways to different drugs, mutations that confer resistance to each drug have to be identified as they develop. Molecular markers cannot predict treatment failure in a patient. However, they can serve as an ‘early warning system’ to identify geographical areas where drug resistance, as observed in patients, is likely to emerge.
In late 2013, a series of mutations to a protein in the *P. falciparum* parasite – Kelch 13 (K13) - were identified as molecular markers associated with delayed parasite clearance in patients treated with artemisinin derivatives in Cambodia.\textsuperscript{10} It is expected that several other mutations are needed, and will occur, before the parasite is fully resistant to artemisinin.\textsuperscript{9,11} It is not yet understood how mutations to the K13 protein cause AR. They could be directly responsible for resistance or they could be changes to compensate for fitness costs caused by other mutations not yet identified.\textsuperscript{9,10} Irrespective of this, the K13 marker is a potentially powerful tool for surveillance in the GMS and beyond.\textsuperscript{10}

**2.3 Where has resistance to ACT been detected?**

Artemisinin drugs normally clear malaria parasites from the blood of a patient within two days of starting treatment. However, increasing numbers of *P. falciparum* infections in western Cambodia, southern Vietnam, eastern Myanmar and western Thailand are now taking up to five days to clear.\textsuperscript{4,39} In some areas, ACTs are starting to fail completely, with persistence of both infection and clinical illness after what should be curative treatment.\textsuperscript{39}

As of January 2014, all countries in GMS had reported some level of resistance to at least one antimalarial.\textsuperscript{8} Table 1 provides a summary of the status of AR in the GMS.

### Table 1: Summary of status of artemisinin resistance in the Greater Mekong Region

<table>
<thead>
<tr>
<th>Country</th>
<th>Suspected year of emergency</th>
<th>Detected 2006</th>
<th>Containment activities started</th>
<th>Artemether-lumefantrine (AL)</th>
<th>Artesunate-mefloquine (AS-MQ)</th>
<th>Dihydro artemisinin-piperaquine (DHA-PPQ)</th>
</tr>
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<tbody>
<tr>
<td>Cambodia</td>
<td>2001*</td>
<td>2009</td>
<td></td>
<td>◆</td>
<td>◆</td>
<td>◆</td>
</tr>
<tr>
<td>Laos</td>
<td>2013</td>
<td>2014</td>
<td></td>
<td>◆</td>
<td>◆</td>
<td>◆</td>
</tr>
<tr>
<td>Myanmar</td>
<td>2001*</td>
<td>2008</td>
<td>2011</td>
<td>◆</td>
<td>◆</td>
<td>◆</td>
</tr>
<tr>
<td>Thailand</td>
<td>2001*</td>
<td>2009</td>
<td>2009</td>
<td>◆</td>
<td>◆</td>
<td>◆</td>
</tr>
<tr>
<td>Vietnam</td>
<td>2009</td>
<td>2009</td>
<td>2011</td>
<td>◆</td>
<td>◆</td>
<td>◆</td>
</tr>
</tbody>
</table>

Legend: \textsuperscript{D3+ = Positive blood slide on Day 3 = Delayed parasite clearance}  
\textsuperscript{TF = Treatment failure}  
\textsuperscript{◆ = >10% cases}  
\textsuperscript{☐ = <10% cases}  
\textsuperscript{Blank = undetermined}  
\textsuperscript{* = detected retrospectively using molecular markers or retrospective data}

With the identification of the K13 mutants, studies have begun this year to evaluate the presence of these molecular markers, throughout the region. In Cambodia, K13 mutants have been found predominantly in the western part of the country with fewer found in the central and eastern areas. Emergence of AR in southern Laos has been confirmed by the recent (2013) identification of the presence of K13 mutants. In Myanmar, studies to evaluate the presence of K13 mutants are ongoing.

2.4. Does drug resistance emerge independently in different areas or does it spread from one area to the next?

*P. falciparum* resistance to chloroquine first emerged in the late 1950s in a low transmission area of western Cambodia. Genetic and epidemiological evidence demonstrates the emergence and subsequent spread of resistance from Southeast Asia to other areas in Asia and subsequently Africa. The same pattern of resistance spread was observed for Sulfadoxine-Pyrimethamine (SP). Indications are that mutations for resistance to chloroquine and SP did not arise independently in Africa, rather resistance spread from the GMS after it emerged and became established there. Within the GMS, mefloquine resistance appeared in Thailand, Cambodia, and Vietnam within five years of its introduction in the 1990s.

Emergence of resistance to artemisinin seems to be following a similar pattern of geographical occurrence to chloroquine and SP resistance, with the primary manifestation currently being described as delayed clearance. Evidence from molecular studies is becoming available now. Indications are that artemisinin drug resistance has emerged independently in multiple sites in GMS rather than spreading from one epicenter. There are no reports of delayed parasite clearance nor has there been the identification of any molecular markers for AR in Africa to date.

3. Health system and social factors that could favour the occurrence of artemisinin resistant malaria

The geographical expansion of drug resistance depends on two things: new resistant mutations emerging, and being selected for; and the transmission of resistant parasites within and between populations. In theory, the establishment of a resistant parasite newly introduced into a population could depend on the amount and nature of drug use in that population, especially if the area is of low malaria transmission. Drug use is affected by a number of health system and social (or supply and demand) factors.

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* Mutations, such as K13, associated with resistance to an antimalarial are referred to as molecular markers.
3.1 Availability of ACTs meeting international quality standards

The availability of good quality antimalarial medicines requires an effective regulatory environment, procurement and distribution system to ensure that quality assured appropriate ACTs enter both the public and private sector supply chains. Data is limited in amount, timeliness, reliability and representativity, but what data is available suggests that an unacceptable proportion of antimalarials available in the GMS are substandard. Substandard drugs can result from legal drug manufacture that has poor quality control or from illegal activity (which may or may not aim to produce an effective product). Substandard drugs could contain too much or too little active pharmaceutical ingredient. Antimalarials containing sub-therapeutic amounts of the active ingredient could potentially increase the risk of the selection and spread of drug-resistant parasites. For combination therapies such as ACT, poor-quality of either one of the drugs leaves the other ‘unprotected’, effectively reducing a combination therapy to a monotherapy.

The continuing availability of monotherapies through the Asia Pacific region poses a further threat to the efficacy of artemisinin. AR could spread more rapidly if it continues to be used as a monotherapy without the protection of an effective partner medicine. In 2006, WHO recommended that artemisinin monotherapy be eliminated. While some countries have enforced a ban, many pharmaceutical companies continue to produce and distribute a variety of artemisinin monotherapies with few regulatory obstacles. Monotherapy with drugs with a long half-life also carries the risk that if a new infection occurs it may expose the parasite to the drug when it has reached sub-therapeutic levels.

3.2 Provider behaviour: proper diagnosis and treatment

Quality antimalarials must be accompanied by quality diagnostics and correct treatment by health workers.

Rapid Diagnostic Tests (RDTs) for malaria are a powerful tool that allows health workers to quickly (within 15 minutes) confirm whether patients are infected with malaria parasites in areas where microscopy is not available or is unreliable. Confirmed diagnosis of malaria, as opposed to clinical diagnosis, is potentially important in low transmission areas to prevent overtreatment of the disease and ‘drug pressure.’ It mitigates the risk of having a large proportion of people with variable concentrations of antimalarial drug in their bloodstream, the consequence of which could be selection for drug resistant forms of the parasite.

However, the introduction of diagnostic tests is challenging. This is mainly because of an unjustified lack of confidence in RDT results in some areas, by health workers and/or patients at all different levels of the health system. At national level, the quality assurance of RDTs is difficult and requires a number of RDTs be sent to regional laboratories of which there are few. This leaves national programs unable to
defend the quality of RDTs if and when there is a perception that they do not perform well, which has been the case in many countries.26 Linked to that, in health facilities, or private pharmacies, health workers are sometimes unsure of the RDT reading and treat patients irrespective of the results.27,28 Even where RDTs are quality controlled, and their use accepted, it is important continuously to monitor that they are being used correctly. Ongoing education of providers and consumers is important.

After diagnosis, proper treatment with the correct dose of a combination of two antimalarials can be challenging if drugs are not co-formulated or pre-packaged together in a well-designed blister pack. This can lead to partial or incomplete ACT. Even with appropriate packaging under-treatment can result from health workers giving a partial course of ACT due to lack of knowledge or pressure from patients, including those who cannot afford the full treatment. Where regulation and quality of care in the private sector is poor there is a higher likelihood that patients will receive monotherapies, substandard antimalarials or partial or incomplete treatment. Each of these could potentially increase the risk of the development of AR.

3.3 Consumer behaviour
Costs to patients of accessing quality diagnosis and antimalarials may be a limiting factor where they are available. Patients may not be able to afford to stop work, travel to a health facility or pharmacy and pay for consultation, diagnosis and an ACT. Even where RDTs and ACTs are provided free-of-charge, patients incur travel costs and user fees, especially in the region’s strong private sector. Cost factors may discourage patients from seeking care or lead them to accept inappropriate or incomplete care.

When patients do have access and can afford quality diagnosis and treatment, they need to complete the full ACT course to reduce the likelihood of resistance developing. There are many reasons why this may not happen. A caregiver or patient may perceive that they have recovered before the dose is complete and decide to safeguard remaining tablets for the next illness in the family.29,30 Caregivers or patients may not understand the instructions for use of the antimalarial or may not have fatty food available (as recommended) each time the drug is due to be taken.29 These are potential causes of parasite exposure to sub-therapeutic doses of antimalarials.

In summary, for a malaria patient to receive the correct treatment for *P. falciparum* malaria a number of supply and demand side factors need to be in place including: the availability of high-quality antimalarials; the lack of availability of sub-standard drugs or monotherapies; adequate knowledge among public and private sector health workers of the correct management of malaria; easy and affordable access to health care; affordability of the high-quality diagnostics and treatment for the patient and; adherence to the antimalarial drug regimen. Figure 1 illustrates how supply and demand side factors can lead to parasite exposure to sub-therapeutic doses of ACT.
*Monotherapy is classified as under-treatment, but it is probably more accurately described as potentially causing direct selection of resistant or partially resistant parasites.*

Source: Developed by the authors from Klein 2013

### 3.4 Population migration and drug resistance

Once a parasite becomes established in one geographical area the likelihood that it will emerge elsewhere depends on the factors described above (if resistance emerges *de novo*) or the amount of migration from the affected area. If a person carrying resistant parasites travels to an area with no resistance and subsequently infects the mosquito population there, whether the resistant parasite
spreads or not is thought to be a function of the proportion of people in that area with antimalarials at sub-therapeutic concentrations in their blood.

Migration within the GMS is a combination of international migration, border mobility and internal migration. Labour migration in GMS is widespread and concerns between three to five million workers. Economic integration in the region has stimulated trade and investment and this in turn has facilitated significant flows of goods, services and people across national borders. Within the region, Myanmar is the major sending country with its migrants concentrated mainly in Thailand and Malaysia. As of 2007, it was estimated that there were about two million Myanmar migrants in Thailand. This amount of movement is worrying in terms of the spread of artemisinin resistant parasites across borders. See box 2 for more detail on why increased migration and trade in the GMS means that AR is an immediate regional and international problem.

Within national boundaries internal migration has also increased significantly. A significant amount of this movement is as a result of urbanisation. However, some is also due to population displacement, internal conflict and associated military movements. These latter two forms of movement are relevant to the containment of AR because of the likelihood that these populations will enter and/or leave higher risk malaria transmission areas.

**Box 2: Why is artemisinin resistance an urgent regional and global problem?**

The emergence and subsequent spread of chloroquine resistance in the 1950s saw the end of the malaria eradication efforts at that time and a resurgence of malaria disease and mortality to levels beyond those seen in the pre-eradication era. Early indications are that AR will follow a similar pattern to that of chloroquine resistance and SP resistance – that is, that it will emerge in the GMS and spread from there, through Myanmar, across India to the east and then through to west Africa. It has the potential to have devastating effects on malaria control efforts worldwide.

The numbers of people travelling both within the region and internationally has increased substantially over the last two decades. Research into international migration has demonstrated a strong connection between migration and infection movement. For example in Bhutan, 77 per cent of all malaria cases originate in three districts located on its southern border with India. Similar connections have been demonstrated inter-continentally for example between Central Asia and West Africa.

For malaria control and elimination strategies to be effective in the region, countries with highly connected populations should give attention to trans-border collaboration, rather than focussing solely on national aims.
4. Progress and Policy

4.1. Progress in addressing artemisinin resistance

A series of documents guide the international response to AR.\textsuperscript{40-43} In addition, in 2012, a Joint Assessment of progress in tackling AR found that “a good, if delayed, start has been made to addressing artemisinin resistance in the GMS” and that “the approach outlined in the Global Plan for Artemisinin Resistance Containment and several associated national level strategies and plans is appropriate.”\textsuperscript{iii} It concluded, however, “\textit{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}.”

Since the Joint Assessment partial progress has been made in a number of areas, for example the establishment of the Emergency Response to Artemisinin Resistance (ERAR) and large contributions from the Global Fund. However, there is startling lack of action in other areas. Most of the

\textsuperscript{iii} The Joint Assessment was carried out in partnership with WHO, Department for International Development (UK) and US Agency for International Development President’s Malaria Initiative, and sponsored by the Australian Agency for International Development, Bill & Melinda Gates Foundation.
recommendations of the Joint Assessment remain valid and even more urgent as evidence emerges of the expansion of resistance in the region. Action to understand and address the underlying causes of this expansion is needed now more than ever.

4.2 Recent developments
Elimination of *P. falciparum* and artemisinin resistance
There is a growing consensus that the most effective, and perhaps only reasonable, approach to preventing geographical expansion of AR is to aim for rapid elimination of *P. falciparum* malaria in the GMS focusing in areas where evidence of resistance (through both TES and molecular studies) has been detected. *P. falciparum* elimination will require the intensification or application of malaria elimination activities to artemisinin hotspots and buffer areas around the epicenter of hotspots. Those activities include scale-up to universal coverage of proven interventions, including those to test, treat and track all cases with active case detection and follow-up. Potential additional activities could also be included such as mass drug administration or rotation of treatments in specific areas where appropriate. These actions should be supported at the national and regional levels to ensure that malaria programs can act rapidly.

Five of the GMS countries have already developed strategies for malaria elimination. These are among 15 countries linked through the Asia Pacific Malaria Elimination Network that are working towards national or sub-national malaria elimination targets. All of these strategies require financial, technical and political support. At the time of preparing this document WHO was initiating the development of a plan for elimination of *P. falciparum* malaria in the GMS.

In addition to accelerating implementation of national malaria elimination strategies more rigorous implementation of two existing WHO recommendations has recently been emphasized:

*Parasitological diagnosis (RDT or microscopy) of all malaria cases before the use of ACT to reduce overtreatment.* This has been policy in most countries for some time but not always fully implemented. Many cases are still treated on the basis of “presumptive diagnosis”. Application of this policy throughout the public and private health sectors would help to reduce excessive, unnecessary use of ACTs.

*Treatment of all *P. falciparum* cases with a single 15mg dose of primaquine in addition to ACT.* While the addition of primaquine to ACTs has been a WHO policy since 2012, there has been slow uptake of policy either due to a lack of political will or a reticence because of previous concerns about safety in the presence of Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency. There is strong evidence for the safety of a single 15 mg dose of primaquine in the treatment of *P. falciparum*. Nevertheless, Phase 1 trials at national level, with cohorts stratified by G6PD deficiency, may be needed to provide local
evidence of the safety of the drug to national programmes, which could prompt them to implement the policy. This may also require the registration of the drug in countries for this purpose.

4.2. Regional Policy Options to support national implementation

The emergence of AR in the GMS is of grave concern especially given early indications of its likelihood to spread beyond current areas and across international borders. Given the real and imminent threat posed by AR to the GMS, Asia Pacific and other regions, the following are recommended as policy options.

Member states of the Asia Pacific region formally advocate WHO for artemisinin resistance to be declared a Public Health Emergency of International Concern.

If AR spreads, it may no longer be possible to reduce malaria transmission or effectively treat malaria cases. Malaria cases, both uncomplicated and severe, would increase significantly and rates of mortality could return to the same or greater than seen pre-2000. As a result, global malaria mortality could increase by 25 per cent. Given this potential impact of AR, it is imperative that countries within the GMS and beyond urgently advocate for a review of the AR situation and declaration of it as a Public Health Emergency of International Concern.

Following is a list of possible policy options for consideration by public health leaders in the region and by the International Health Regulations Emergency Review Committee:

Strengthen cross-border collaboration for surveillance of artemisinin resistance.

The detection and delineation of the artemisinin resistance problem is key to how responses are shaped. Surveillance needs to be prioritised as does information sharing across borders. Activities that are already underway, for example testing for the K13 molecular marker and TES need to be supported, and enhanced where necessary.

Ensure adequate supply of quality diagnostics and therapeutics to meet regional needs.

A secure supply of high quality efficacious ACTs and RDTs in the region relies on strong collaboration with the pharmaceutical sector from planning for new antimalarials, forecasting needs through to quality assurance at point of care. ACTs are the last line of antimalarials and as such there is an urgent need to develop alternatives, or ideally a malaria vaccine. Regional collaboration with the pharmaceutical sector on research and development is essential. In addition, APLMA could promote regional manufacturers to be supported to go through the WHO prequalification process. Ensuring good
manufacturing practices in the region should, in theory, lead to the replacement of substandard ACTs with high-quality products of increased affordability due to increased competition.

**Strengthen national regulatory capacity and enforcement to ensure quality of antimalarial drugs and diagnostics**

Fake drugs kill, and monotherapies or substandard drugs could accelerate the emergence of artemisinin resistance. Halting the manufacture, distribution and use of oral artemisinin monotherapies and the removal of fake and substandard medicines from the region are high priorities. Only limited resources exist regionally to measure the quality of RDTs. It would be useful to have adequate continuous regional capacity to assure the quality of RDTs and future diagnostic products.

**Develop and implement a program of prequalification of primaquine products and ensure registration of their use in countries as a single 15mg dose for prevention of transmission**

Adding primaquine to ACTs could help to slow the emergence of artemisinin resistance. However before this is possible, a number of constraints need to be addressed. These include: primaquine’s registration status; a limited numbers of pre-qualified manufacturers; and lack of designated regional laboratories for quality control.

**Increase regional collaboration for a more agile and aggressive response to artemisinin resistance**

In addition to intensification of standard malaria control measures, *extraordinary* measures should be considered in “hotspots” of AR, including those where the K13 molecular marker has been identified. Given the urgency of the issue, decisions need to be based on the best evidence available, while concurrently investing in the generation of evidence on specific questions.

Regional collaboration could include:

- Agreement on standardised protocols on, for example: the use of mass drug administration; rapid adaptation and possibly rotation of treatment protocols; more consistent delineation of “hotspots” and “buffer zones”, standard protocols for case investigation, etc.
- A rapid response taskforce to support countries with emergency responses or policy implementation challenges, for example: responding to new foci of resistant malaria; implementing changes to first line therapy or adding primaquine to standard treatment. This should be a function of the WHO ERAR hub in Phnom Penh but the current level of capacity and response suggests this may need substantial support.
Answer priority local research questions urgently, as they arise
There is an immediate need for a small but highly flexible funding mechanism for rapid grants to research on urgent operational bottlenecks, e.g. alternative ACT dosage regimens.

Strengthen cross-border and multisectoral collaboration in priority areas
Effective and sustainable elimination of *P. falciparum* malaria, and specifically artemisinin resistance, requires concerted coordinated efforts of multiple sectors (See Annex 1), globally, regionally and across inter- and intra-national boundaries. Existing regional initiatives, for example Association of Southeast Asian Nations (ASEAN or ASEAN+), could be mapped, built upon and more adequately financed if necessary. Where multi-sectoral cross-border mechanisms are not in place, short, time-limited high-level taskforces could be created to address specific issues relevant to artemisinin resistance.

Track and respond to progress on artemisinin resistance continuously
APLMA as a regional collaboration mechanism, and by mutual consent among its members, could help to hold countries accountable for their progress in the implementation of commonly agreed measures for the detection and elimination of AR. To ensure objectivity and responsiveness, verification of progress could be done by an independent group such as the Independent Monitoring and Support Group proposed under the Global Fund’s Regional Artemisinin Initiative.
Annex 1
Examples of some important social and environmental determinants for artemisinin resistance by level and potential sector matches (taken from Roll Back Malaria Multisectoral Action Framework for Malaria, 2013)

| Examples of some determinants for Artemisinin Resistance by analytical level (e.g. society, environment etc) | Foreign affairs & international cooperation | Finance & economy | Food & Agriculture | Trade, industry etc | Infrastructure, Transport and works | Education | Social Protection | Justice | Science & Tech | Environment | Water & Sanitation | Information | Community development | Health | Public Admin, including local government |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. Society | | | | | | | | | | | | | | | | |
| Demographic change: structural population movements | | | | | | | | | | | | | | | | |
| Governments ability to regulate | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | |
| Organisation of societies and services | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | |
| 2. Environment | | | | | | | | | | | | | | | | |
| Economic development projects | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | |
| 3. Population group | | | | | | | | | | | | | | | | |
| Population mobility (internal and international) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | |
| Occupation | | | | | | | | | | | | | | | | |
References


