MEETING ON ADDRESSING URGENT ISSUES PERTAINING TO ANTIMALARIAL DRUG MANAGEMENT TO FACILITATE ACCELERATED ELIMINATION OF MALARIA FROM THE GMS COUNTRIES OF THE WESTERN PACIFIC REGION

26–28 February 2018
Phnom Penh, Cambodia
MEETING REPORT

MEETING ON ADDRESSING URGENT ISSUES PERTAINING TO ANTIMALARIAL DRUG MANAGEMENT TO FACILITATE ACCELERATED ELIMINATION OF MALARIA FROM THE GREATER MEKONG SUBREGION COUNTRIES OF THE WESTERN PACIFIC REGION

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26–28 February 2018

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NOTE

The views expressed in this report are those of the participants of the Meeting on Addressing Urgent Issues Pertaining to Antimalarial Drug Management to Facilitate Accelerated Elimination of Malaria from the GMS countries of the Western Pacific Region and do not necessarily reflect the policies of the conveners.

This report was prepared by the World Health Organization Regional Office for the Western Pacific for Member States in the Region and for those who participated in the Meeting on Addressing Urgent Issues Pertaining to Antimalarial Drug Management to Facilitate Accelerated Elimination of Malaria from the GMS countries of the Western Pacific Region in Phnom Penh, Cambodia, from 26 to 28 February 2018.
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Keywords:
Antimalarials / Health Policy / Malaria - epidemiology, prevention and control / Mekong valley
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>ACT</td>
<td>artemisinin-based combination therapy</td>
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<tr>
<td>CIP</td>
<td>Coalition of Interested Partners</td>
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<tr>
<td>CNM</td>
<td>National Center for Entomology, Parasitology and Malaria Control (Cambodia)</td>
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<tr>
<td>CoRE</td>
<td>Centre of Regulatory Excellence</td>
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<td>DDF</td>
<td>Department of Drugs and Food (Cambodia)</td>
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<td>DER</td>
<td>Drug and Efficacy Response</td>
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<tr>
<td>DFAT</td>
<td>Australian Government Department of Foreign Affairs and Trade</td>
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<tr>
<td>EML</td>
<td>essential medicine list</td>
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<td>EMP</td>
<td>Essential Medicines and Health Products</td>
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<tr>
<td>EMT</td>
<td>Essential Medicines and Health Technologies</td>
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<tr>
<td>G6PD</td>
<td>Glucose-6-phosphate dehydrogenase</td>
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<td>Global Fund</td>
<td>Global Fund to Fight AIDS, Tuberculosis and Malaria</td>
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<td>GMP</td>
<td>Global Malaria Programme</td>
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<td>GMS</td>
<td>Greater Mekong Subregion</td>
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<td>GTS</td>
<td><em>Global Technical Strategy for Malaria 2016–2020</em></td>
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<td>iDES</td>
<td>integrated drug efficacy surveillance</td>
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<td>MME</td>
<td>Mekong Malaria Elimination</td>
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<td>MVP</td>
<td>Malaria, other Vectorborne and Parasitic Diseases</td>
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<td>NMP</td>
<td>national malaria programme</td>
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<td>NRA</td>
<td>national regulatory authority</td>
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<td>NTG</td>
<td>national treatment guideline</td>
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<td>oAMT</td>
<td>oral artemisinin monotherapy</td>
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<tr>
<td>RDT</td>
<td>rapid diagnostic test</td>
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<td>RRP</td>
<td>Regional Regulatory Partnership</td>
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<td>RSM</td>
<td>rapid supply mechanism</td>
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<td>RSS</td>
<td>Regulatory Systems Strengthening</td>
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<td>SRA</td>
<td>Stringent Regulatory Authority</td>
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<td>TES</td>
<td>therapeutic efficacy studies</td>
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<td>TGA</td>
<td>Therapeutic Goods Administration</td>
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<tr>
<td>UNOPS</td>
<td>United Nations Office for Project Services</td>
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<tr>
<td>USP</td>
<td>United States Pharmacopeia</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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SUMMARY

Accelerated malaria elimination in the Greater Mekong Subregion (GMS) countries requires the availability and full implementation of updated national treatment guidelines (NTGs) based on the latest therapeutic efficacy studies (TES). The rapid decline of malaria cases following concerted efforts at elimination of multidrug-resistant forms of falciparum has presented new challenges. Among these challenges, the following two are the most important: the continued evolution of resistance requiring the regular updating of first- and second-line antimalarial medicines for foci of resistance; and the sourcing of increasingly small quantities of these drugs within a short time frame to ensure full implementation of revised guidelines in these foci.

Recent experience has demonstrated that NTGs can be updated rapidly by ministries of health for the management of resistant foci; however, their implementation is delayed due to regulatory challenges faced when importing new artemisinin-based combination therapies (ACTs) and problems in procuring small quantities of new ACTs for use in such foci. Full implementation of WHO recommendations on the use of primaquine to arrest the spread of falciparum malaria and the problem of relapses in vivax malaria due to poor compliance with primaquine regimens also remain challenging. As recommended by the World Health Organization (WHO), a virtual limited stockpile of ACTs has been initiated by the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) to expedite country access to antimalarial medicines. Now, countries are encouraged to utilize the rapid supply mechanism (RSM) and ensure no delays occur in sourcing new ACTs for management of malaria in resistant foci. In the August 2017 meeting on WHO malaria treatment guidelines in the Western Pacific, problems associated with updating NTGs to address effective management of malaria in resistant foci, addressing regulatory constraints and procuring small quantities of new ACTs to use in resistant foci were identified as challenges requiring urgent solutions.

The Malaria, other Vectorborne and Parasitic Diseases (MVP) unit of the WHO Regional Office for the Western Pacific coordinated this meeting, bringing together representatives from ministries of health, staff from national malaria programmes, procurement divisions and national regulatory authorities (NRAs) to: identify appropriate first line treatments for management of malaria in resistant foci and possible alternatives based on current TES data; agree on a mechanism for accessing the RSM of antimalarial medicines; discuss regulatory constraints to fully implementing updated malaria treatment policies; and address the continuing challenge of availability of substandard ACTs and artemisinin monotherapies in Western Pacific Region countries of the GMS.

Conclusions:

1. Countries of the GMS have made considerable progress towards updating their NTGs and have done considerably well to prevent the emergence of new foci of resistance.
2. Updated NTGs are not fully operationalized in most GMS countries, particularly related to the availability and use of second-line treatments for uncomplicated malaria and with implementation of primaquine regimes for all forms of malaria.
3. Only first-line ACTs are registered in most GMS countries, resulting in significant delays in accessing second-line or alternative ACTs, particularly for treatment in foci of resistance.
4. In some instances, significant delays in implementing NTGs (updated first-line treatments) after resistance was detected likely contributed to exposing resistant parasite populations to suboptimally effective ACT regimens for several months, possibly leading to greater resistance levels in these parasite populations. However, it is noteworthy that these implementation delays have not been associated with increased mortality.
5. Countries of the GMS have continued to strengthen TES for antimalarial medicines, particularly in the Lao People’s Democratic Republic; however, ACTs being subjected to TES are limited in number, which restricts the ability of countries to make informed choices about optimal treatment regimens.
6. Quantification of antimalarial medicines in most GMS countries is determined based on...
historical epidemiological data rather than current transmission dynamics, resulting in
treatment supply management challenges and a need for antimalarial medicine redistribution
in the periphery.

(7) The Global Fund has established the RSM to provide grant recipient countries quick access to
antimalarial medicines. However, all ACTs are not yet available under the RSM. The
availability of ACTs under the RSM alone is not adequate as national drug registration and
other regulatory requirements must also be met.

(8) As presented at the meeting, some WHO prequalified or registered antimalarial medicines in
the GMS have tested non-conformant to international standards in post-market quality testing.
Pre-shipment testing was not conducted on most of the antimalarial medicines tested, and
therefore it is difficult to determine if substandard products were due to manufacturing issues
or degradation along the supply chain. Follow up investigations were proposed.

(9) National regulatory authority capacity and regional regulatory partnership mechanisms are
not adequately supported or funded in most GMS countries, leading to the inability of
countries to accelerate the introduction of appropriate antimalarial medicines.

Recommendations for Member States

(1) Update NTGs based on the latest TES results and expedite full operationalization of revised
treatment guidelines for first- and second-line therapies and primaquine regimes for all forms
of malaria, including development of necessary bench aids and clinician trainings.

(2) Expand TES in all GMS countries in the Western Pacific Region to include currently
available, effective ACTs.

(3) Acknowledging problems associated with accessing small quantities of new ACTs, countries
are encouraged to access such requirements through the RSM established by the Global Fund;
however the RSM should not be viewed as a solution for inadequate planning during routine
procurement and supply management processes.

(4) National malaria control programme staff and supply management staff are encouraged to
work closely together and use strengthened surveillance data to more accurately quantify and
distribute antimalarial medicines, including ACTs.

(5) Accelerate efforts to strengthen core regulatory functions by: (a) adopting mechanisms to
accelerate the registration of priority treatments (all ACTs) and diagnostics, including through
WHO collaborative procedures and Stringent Regulatory Authorities (SRAs)–facilitated
registration; and (b) strengthening post-market and vigilance functions to ensure access to
safe and quality-assured antimalarial medicines.

Recommendations for WHO.

(1) Support national malaria control programmes to update their NTGs and to fully operationalize
said guidelines, including primaquine treatment for all forms of malaria.

(2) Support country expansion of TES to include all currently effective ACTs and support field
testing of integrated drug efficacy surveillance (iDES) in select areas of low malaria
transmission.

(3) Support implementation of need-based access to the Global Fund's RSM and support
countries to address regulatory constraints related to rapid access of antimalarial medicines
through RSM.

(4) Support the identification of procurement bottlenecks for WHO prequalified or registered
products while encouraging pre-shipment and post-marketing quality testing.

(5) Encourage strengthening of quantification for treatment supply management; support
strengthening of malaria epidemiological surveillance to better quantify antimalarial medicine
requirements based on transmission dynamics rather than historical data.

(6) Support strengthening of regulatory authorities to register all available ACTs and to expand
pharmacovigilance and quality assurance of antimalarial medicines.

(7) Encourage investments to strengthen national regulatory authority capacity and regional
regulatory partnership mechanisms.
(8) Promote coordinated, prioritized support for regulatory system strengthening in conjunction with other technical partners, in particular to expedite access to antimalarial medicines and new products for malaria control.

(9) Support the Global Fund to ensure availability of all antimalarials, especially WHO prequalified ACTs in the RSM.
1. INTRODUCTION

1.1 Background

Accelerated malaria elimination in GMS countries requires availability and full implementation of updated NTGs based on the latest available TES data. The rapid decline in malaria cases following concerted efforts at elimination of multidrug-resistant forms of falciparum has presented new challenges. Resistance evolves requiring regular updating of first- and second-line antimalarial medicines for foci of resistance, and the sourcing of increasingly small quantities of these drugs within a short time frame to ensure full implementation of revised guidelines in these foci.

Recent experience has demonstrated that NTGs can be updated rapidly by ministries of health for the management of resistant foci; however, their implementation is delayed due to regulatory challenges faced when importing new ACTs and due to problems faced in procuring small quantities of new ACTs for use in such foci. Additionally, full implementation of WHO recommendations on the use of primaquine to arrest the further spread of falciparum malaria and the problem of relapses in vivax malaria has been challenging. As recommended by WHO, a virtual stockpile of ACTs has been initiated by the Global Fund to expedite country access to antimalarial medicines. Countries are encouraged to move the RSM forward and ensure no delays in sourcing new ACTs for management of malaria in resistant foci. In the August 2017 meeting on WHO malaria treatment guidelines in the Western Pacific, problems associated with updating NTGs to address effective management of malaria in resistant foci and addressing regulatory constraints and procuring small quantities of new ACTs for use in resistant foci were highlighted as challenges requiring urgent solutions.

This meeting, organized by the Malaria, other Vectorborne and Parasitic Diseases (MVP) unit of the WHO Regional Office for the Western Pacific brought together representatives from ministries of health, staff from national malaria control programmes, procurement divisions and national regulatory authorities to: identify appropriate first line treatments for management of malaria in resistant foci and possible alternatives based on current TES data; agree on a mechanism for the setting up the RSM virtual limited stockpile of antimalarial medicines; discuss regulatory issues in implementing malaria treatment policies; and address the continuing challenge of availability of substandard ACTs and artemisinin monotherapies in the GMS.

1.2 Objectives

The objectives of the meeting were:

1) to update national malaria treatment guidelines based on latest results following TES;
2) to address implementation challenges in the full operationalizing of NTGs through effective drug management and addressing the challenge of continuing availability substandard ACTs and monotherapies; and
3) to facilitate full operationalizing of NTGs, improving access to antimalarial medicines, including new ACTs for management of malaria in resistant foci.

1.3 Opening remarks

Dr Yunguo Liu, WHO Representative to Cambodia, delivered the welcome address on behalf of Dr Shin Young-soo, WHO Regional Director for the Western Pacific. He emphasized that countries in the Western Pacific must strengthen efforts to stay on track and meet national targets for elimination by 2030. Given the continuing emergence and spread of resistance of *Plasmodium falciparum* to artemisinin and some of its partner medicines in the region, it is critically important to constantly monitor the efficacy of antimalarial medicines. Dr Liu noted that even though the countries in the GMS have progressively updated their treatment policies based on TES, the region continues to
experience challenges for best managing antimalarial medicine through strengthened regulatory procedures and expedited means of procurement and delivery of these medicines. He concluded by thanking the participants for taking the time and effort to attend this important meeting.

1.4 Nomination of chair, vice-chair and rapporteur and administrative announcements

On behalf of the Regional Director, Dr Hiromasa Okayasu, Coordinator for the Mekong Malaria Elimination (MME) Initiative, presided over the election of the officers for the meeting. Dr Rattanaxay Phetsouvanh, Deputy Director General, Department of Communicable Diseases Control, Ministry of Health in the Lao People’s Democratic Republic, was nominated as chair. Dr Lek Dysoley, Deputy Director, National Center for Entomology, Parasitology and Malaria Control in Cambodia, was nominated as vice-chair. Dr Nguyen Quang Thieu, Deputy Director, National Institute of Malariology, Parasitology and Entomology in Viet Nam, was nominated as rapporteur. The nominations were endorsed by all participants.

It was noted that there were no conflicts of interest among the participants and temporary advisers as per completed conflict of interest forms submitted to the Secretariat.

The meeting agenda is included in Annex 1, and the list of participants in Annex 2.

2. PROCEEDINGS

2.1 Session 1: Overview of global and regional malaria treatment guidelines

2.1.1 Updates on artemisinin resistance and guidance for the current WHO treatment policies including treatment options in foci of resistance in the GMS

Dr Pascal Ringwald, Coordinator, Drug and Efficacy Response (DER), Global Malaria Programme (GMP) presented on the threat of antimalarial drug resistance, beginning with a brief history of artemisinin, its mode of action and the risk of treatment failures using monotherapies. The range of standard treatments for

\[ P. falciparum \]

uncomplicated malaria include artemether–lumefantrine (AL), artesunate–amodiaquine (AS-AQ), artesunate–mefloquine (AS-MQ), artesunate–sulfadoxine-pyrimethamine (AS-SP), dihydroartemisinin–piperazine (DHA-PIP) and artesunate–pyronaridine (AS-PYR). The standard treatments for severe \[ P. falciparum \] malaria include injectable artesunate, artemether or quinine followed by a full course of ACT. Dr Ringwald then defined a number of WHO concepts and terms surrounding drug resistance.

- **Antimalarial resistance** is defined as the ability of a parasite strain to survive and/or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended but within tolerance of the subject.
- **Artemisinin resistance** is defined as delayed parasite clearance following treatment with an artesunate monotherapy or with an ACT (partial resistance/tolerance is better wording).
- **Multidrug resistance** requires resistance to more than two operational antimalarial compounds of different chemical classes.
- **Treatment failure** is the inability to clear parasites from a patient’s blood or to prevent their recrudescence after the administration of an antimalarial. Many factors can contribute to treatment failure, including incorrect dosage, poor patient compliance, poor drug quality, and drug interactions and resistance. Most of these factors are addressed by TES.

In reporting the findings of therapeutic efficacy tests, the term ACT resistance is imprecise. He noted that rather, ACT treatment failure, defined as treatment failure following treatment with an ACT regardless of the presence of artemisinin resistance, is a more appropriate term that notes the specific
ACT and the nature of the resistance if confirmed (meaning artemisinin partial resistance/tolerance or partner drug resistance, or both). The consequences of artemisinin partial resistance were explained. Artemisinin resistance affects only ring stages of *P. falciparum* which has implication for the treatment of severe malaria (so far mortality increases have not been reported). In the absence of partner drug resistance, ACTs are highly efficacious. Dr Ringwald noted an example that partial artemisinin resistance did not facilitate the emergence of mefloquine and piperaquine resistance (both already present in the GMS), but it may have facilitated, among many other factors, the rapid spread of a lineage carrying both resistance to artemisinin and to piperaquine. He then presented data to demonstrate reduced efficacy of DHA-PIP in Cambodia against K13 mutant parasites. Throughout the GMS, ACT failures are highest in Cambodia, currently showing high failure rates (>10%) to four ACTs. With the spread of antimalarial drug resistance to Viet Nam and other countries in the GMS, cross-border collaboration remains a high priority in the region.

WHO presented a simple but strong message during the discussion, emphasizing that countries should only use antimalarial medicines that are efficacious. Ensuring effective medicines requires national programmes to continue studying efficacy of first-line antimalarial drugs, and to also study the efficacy of potential replacement ACTs. Dr Ringwald shared that Cambodia, did not have access to AS-MQ for many months and had to continue using DHA-PIP, likely leading to drug resistance spreading. Dr Abeyasinghe also emphasized the importance of drug management and reiterated that using less-than-efficacious drugs leads to the spread of resistance strains, making them more resilient and hard to eliminate. Reduced sensitivities mean that previously effective drugs must be removed. He also noted that in Cambodia, it took far too long for the programme to change their drug policy and operationalize implementation of a new, more effective drug. He noted that this meeting was called to improve access and approvals by donors and for countries to remove drugs that are not efficacious. Also discussed were options for alternative drug regimens, such as providing two ACTs for malaria but this would require longer treatment periods which are difficult for patients and currently not feasible.

### 2.1.2 Overview of the malaria situation in Cambodia, the Lao People’s Democratic Republic and Viet Nam

Dr Okayasu provided an update of the malaria situation in the GMS from the perspective of the MME Initiative. Introducing a brief background, he highlighted Cambodia’s introduction of ACTs on a national scale in 2000 and early warning signs of *P. falciparum* resistance to artemisinin being detected in 2006 along with reports of resistance along the Cambodia–Thailand border in 2008. Since then, *P. falciparum* resistance to artemisinin has been detected in five countries in the GMS, including Cambodia, the Lao People’s Democratic Republic, Myanmar, Thailand and Viet Nam. To combat the emergence of artemisinin resistance, GMS countries have adopted the following strategies and targets.

- **By 2020 or earlier**, transmission of *P. falciparum* malaria should be interrupted in all areas of multidrug resistance, including ACT resistance.
- **By 2020**, *P. falciparum* malaria is to be eliminated in Cambodia and all species of human malaria to be eliminated from Yunnan Province, China.
- **By 2025**, *P. falciparum* malaria is to be eliminated in all countries of the GMS and all species of human malaria to be eliminated in Cambodia and Thailand.
- **By 2030**, all species of human malaria is to be eliminated in all countries of the GMS.

The presenter highlighted the progress made to date in the GMS, including a 74% reduction in the number of malaria cases from 2012 to 2016 and a 41% reduction in the number of malaria cases from 2015 to 2016. However, challenges remain. In 2017, the number of malaria cases increased in Cambodia and Viet Nam, almost doubling in Cambodia from approximately 23,000 confirmed positive cases in 2016 to over 46,000 in 2017, and increasing only slightly in Viet Nam during the same time period from 4100 cases to over 4500 cases. Most of the cases reported in 2017 in Cambodia and Viet Nam occurred between September and December. In the Lao People’s
Democratic Republic, most cases are reported from five southern provinces, and in Viet Nam, most cases are reported from seven central highland provinces.

Dr Okayasu emphasized that to achieve targets in the GMS, a political commitment and sustainable funding are required, along with strong implementation of activities, addressing drug resistance and improving malaria surveillance. As countries in the GMS continue to be the epicentre of antimalarial drug resistance and recent studies demonstrate high ACT failure rates (four ACTs failing in Cambodia), it is urgent that countries review their treatment guidelines regularly and update accordingly. The major issues in the GMS surrounding drug resistance and drug quality are the presence of substandard products, continued use of artemisinin monotherapies and lack of sufficient capacity of NRAs. Under the second phase of the Global Fund’s Regional Artemisinin-resistance Initiative, also known as the RA12 Elimination Programme or RA12E, WHO will provide support to GMS countries to strengthen their capacities to prevent, detect and respond to substandard and falsified products; to develop national legal frameworks to address substandard and falsified products; to implement a risk-based market surveillance system; to foster cross-border collaboration at bilateral and trilateral levels; and to advocate against substandard and falsified products.

2.1.3 Current national treatment guidelines in Cambodia, the Lao People’s Democratic Republic and Viet Nam

Dr Rabindra Abeyasinghe, Coordinator, MVP, presented a technical update on strategies for malaria elimination in the GMS and summarized the NTGs of Cambodia, the Lao People’s Democratic Republic and Viet Nam. He also reviewed TES data in the GMS. The presenter noted that apart from the goal of eliminating malaria in the GMS by 2030 and the elimination of *P. falciparum* by 2025, it is important to plan in advance to prevent the re-introduction of malaria after elimination has been achieved. He emphasized that national programmes in Cambodia, the Lao People’s Democratic Republic and Viet Nam must respond aggressively to eliminate malaria in areas with multidrug resistance (including ACT).

In 2017, Cambodia began its nationwide implementation of AS-MQ and decided to introduce low-dose primaquine as first-line treatment for *P. falciparum*. The 2016 TES results demonstrated treatment failures at Day 3 for DHA-PIP, while AS-MQ was shown to be completely effective. In the Lao People’s Democratic Republic, AL plus low-dose primaquine are used to treat *P. falciparum* and a pilot is planned to test AL plus primaquine (14 day) for *P. vivax* (with G6PD test). Quinine and doxycycline plus single-dose primaquine was adopted in 2016 as second-line treatment of uncomplicated *P. falciparum*. Results are pending for the 2016–2017 TES in the Lao People’s Democratic Republic, but results from 2014–2015 demonstrated 10% treatment failure of AL after Day 3 with 87% of samples tested having K13 mutant (C580Y and R539T). In Viet Nam, first-line treatment for uncomplicated *P. falciparum* is DHA-PIP and second-line treatment is quinine plus doxycycline for seven days or quinine plus clindamycin for seven days. First-line treatment for *P. vivax* is chloroquine for three days. Most recent TES results for DHA-PIP demonstrated 25% treatment failure at Day 3 and 54% sensitivity in Bin Phuc. TES results are pending for AS-PYR (pyramax). An iDES pilot is planned for 2018.

The presenter continued to discuss the core principles of reducing drug resistance. Early diagnosis and prompt effective treatment within 24–48 hours of the onset of malaria symptoms are critical. Rational use of antimalarials to reduce the spread of drug resistance, limit wastage, and ensure effective case management of febrile illnesses must be ensured, as well as universal access to parasitological diagnosis. Combination therapy is important to improve efficacy and prevent or delay resistance, while appropriate weight-based dosing will prolong the useful therapeutic life of antimalarial medicines. For uncomplicated malaria, the therapeutic objectives are to: cure the infection as rapidly as possible to ensure elimination of the malaria parasites that caused the treated infection and to prevent progression to severe disease; reduce transmission thereby reducing infectious reservoirs; and prevent emergence and spread of antimalarial drug resistance.
It is critical that antimalarial drug quality is ensured. This can be achieved by providing support to national drug and regulatory authorities and by ensuring antimalarial medicines provided in both private and public sectors are of acceptable quality through regulation, inspection and law enforcement. Preventing the availability and use of oral artemisinin monotherapies and ensuring that counterfeit/falsified and substandard antimalarials are not in the market are important. Also, antimalarial drug manufacturers providing medicines should be prequalified. Regular conduct of TES of antimalarial drugs using standard WHO protocols must be done. To ensure that quality antimalarial medicines are available, the national malaria programmes (NMPs) should monitor implementation and impact of new malaria treatment recommendations and detect decreasing antimalarial efficacy and drug resistance as early as possible. NMPs and regulatory bodies can promote rational use of antimalarial medicines by limiting unnecessary use of antimalarial drugs (test before treating) and promoting adherence to a full treatment course.

Dr Abeyasinghe noted the importance of providing universal diagnostic testing for all suspected malaria cases. He noted that all patients who are suspected of having malaria should have the diagnosis confirmed by parasite detection methods such as quality-assured microscopy or rapid diagnostic test (RDT). Both public and private sector health services should confirm the diagnosis before administering antimalarial treatment and every confirmed case should be tracked and reported in the surveillance system in order to inform programme planning. Ensuring universal diagnostic testing will reduce the overuse of ACTs, the first-line treatment for uncomplicated malaria, and reduce the drug pressure on parasites. Community-based case management should also be considered as a means to improve access to prompt effective treatment of malaria episodes by trained community members living as close as possible to the patients.

During the discussion, Dr Abeyasinghe emphasized the need to operationalize low-dose primaquine for *P. falciparum*. He emphasized that there is no need to confirm the presence or absence of G6PD deficiency, as the low, single dose of primaquine will not result in severe haemolysis. Viet Nam noted that TES for AS-MQ is planned, given that DHA-PIP resistance is occurring in Bin Phuc and Dak Lak provinces where the burden remains high and early diagnosis before providing treatment was emphasized. The United Nations Office for Project Services (UNOPS) stated that to avoid delays of AS-MQ implementation in Cambodia, registration of alternative antimalarial drugs should be done well in advance and that better management of manufacturers is required, including the ability to procure smaller quantities.

### 2.2 Session 2: Regulatory frameworks for elimination settings: progress to date

#### 2.2.1 Update on the coalition of WHO and interested partners supporting regulatory systems strengthening and its work in the GMS

Dr Mike Ward, Coordinator, Regulatory Systems Strengthening (RSS), Essential Medicines and Health Products (EMP), WHO headquarters, presented details on a "Coalition of Interested Partners" (CIP) supporting regulatory systems strengthening and its work in the GMS. He initially highlighted the shared purpose of regulatory strengthening, including the promotion of timely access and appropriate use of malaria treatments to accelerate malaria elimination. Noting that this is a complex objective requiring sustained support and coordination from key state and non-state actors, he also suggested that regulatory strengthening is enabled by strong political support. Shared interests, including malaria elimination, regional health security and strengthened regulatory systems, bring together NMPs, ministries of health, NRAs, donors, procurement agencies, WHO, technical development partners and industry.

Regulatory oversight at the global level includes the evaluation of drug quality, efficacy and safety. Some elements of regulatory oversight must remain local, including licensing decisions, local manufacturing oversight, pharmacovigilance, appropriate distribution controls (stability and cold chain), and product security (substandard and falsified products). Flexibility must be inherent in the
system. Regulatory oversight must be risk-based to achieve a balance between appropriate controls and timely access to medical products. Circumstances will arise where accelerated access is warranted, such as during emergencies of public health concern, during drug shortages and when there are innovations in treatment of critical illness. A spectrum of risk-based options could include waivers, accelerated evaluation pathways or provisions to accept expert recommendations.

Dr Ward presented how WHO is working to accelerate access to quality medical products, including systematically supporting regulatory systems strengthening, Good Regulatory Practices, building stronger networks for harmonization, convergence and work-sharing, facilitating product reviews and registration, and supporting a stronger prequalification programme. WHO has established the CIP framework to achieve better coordination, efficiency and outcomes in regulatory strengthening activities in the same target Member States or regions to achieve better public health outcomes. A series of discussions has taken place at the global level, most recently in June 2017, to establish the coalition, involving many of the same organizations that form part of the Regional Regulatory Partnership (RRP) for Malaria Elimination. Country pilots have been done to provide experience at operational level and discussions held around regional and function “chapters”. WHO foresees RRP as a regional chapter of the CIP, similar to the situation in Africa.

Dr Ward discussed the RRP strategy. The strategy and country work plans place priority on facilitating registration of quality-assured malaria treatments and diagnostic tests while providing balanced support for other targeted regulatory activities, notably vigilance and post-market control. The strategy takes advantage of existing networks, instruments and activities and work plans developed jointly with and valued by countries. Proposed activities should be prioritized based on risk and relevance to the malaria elimination goal. Shared responsibility among partners and countries is divided into short-, medium- and long-term activities. Immediate next steps were presented, including the need to finalize prioritization of activities, joint planning to establish how partners will share work and in parallel, establish CIP to facilitate work of RRP, including through the sharing of information and coordination of activities.

Common identified gaps and proposed activities were presented for three RRP categories including registration and marketing authorization, vigilance and market surveillance and control. Identified gaps included: no legal provisions to recognize decisions, reports or information from other NRAs or regional or global bodies; no mechanism for joint assessments; and a risk-based evaluation concept is lacking, including fast track registration. Corresponding proposed activities included: capacity building in reviewing dossiers and applications for generic medicines and diagnostics using facilitated pathways; and implementation of a mechanism for a fast track procedure, guidelines and protocols. In conclusion, the ultimate imperative is to accelerate access to malaria treatments and diagnostics while providing adequate support for other important regulatory activities, notably vigilance and safety monitoring and market surveillance and control that together will help ensure the quality and appropriate use of priority products in the context of strengthening the regulatory systems in target countries.

2.2.2 Update on pharmaceutical system strengthening work in the GMS

Ms Uhjin Kim, Technical Officer, Essential Medicines and Health Technologies (EMT), WHO Regional Office for the Western Pacific presented updates surrounding the main activities implemented under Regional RAI Pharma Grant, including assessment of the malaria supply chain in the GMS; the rational drug use survey in Cambodia and the Lao People’s Democratic Republic; surveillance on quality, source, and prevalence of antimalarial medicines in the GMS; and the GMS workshop on regulatory actions to counter substandard and falsified medicines held on 25–27 April 2017 in Bangkok, Thailand.

An assessment of malaria supply chains was done in five countries, namely, Cambodia, the Lao People’s Democratic Republic, Myanmar, Thailand and Viet Nam, with in-country missions held from August to October 2016. All countries endorsed the final report in February 2017, which was

The rational drug use survey in Cambodia and the Lao People’s Democratic Republic was a facility-based fever management survey in the public and private sectors in the Lao People’s Democratic Republic and public sector in Cambodia. The survey was conducted in five provinces in each country (seven districts in Cambodia and nine districts in the Lao People’s Democratic Republic). Fifty health-care providers were interviewed in each country, and 12 patients in Cambodia and 104 patients in the Lao People’s Democratic Republic were surveyed. The inception meeting with national officials was held on 24–25 October 2016, and WHO Regional Office for the Western Pacific ethical committee approval was granted in February 2017. Data were collected from February to May 2017 in the Lao People’s Democratic Republic and from July to November 2017 in Cambodia.

Several findings from interviews with health-care providers were reported. Diagnostic services were available at almost all health facilities (RDT availability: 100% in Cambodia and 94% in the Lao People’s Democratic Republic), and RDT was the most commonly used diagnostic method over microscopy. Regarding knowledge, most of the facilities had malaria treatment guidelines and recorded malaria patients treated at the facility level (86% in Cambodia and 98% in the Lao People’s Democratic Republic). The majority of health-care providers had been trained on malaria diagnosis and treatment (88% in Cambodia and 94% in the Lao People’s Democratic Republic). While the majority of health-care providers were aware of the issue of artemisinin resistance in the Lao People’s Democratic Republic (86%), only about half were aware in Cambodia (46%). In terms of prescription patterns, most health-care providers always tested fever patients before prescribing antimalarial medicines and antipyretics in both countries. Also, most providers had accurate knowledge about the first-line treatment of malaria. A gap was observed regarding second-line treatment and management of severe malaria cases and management of malaria-negative fever patients.

A number of findings were reported regarding treatment-seeking behaviour of the fever patients. The number of patients seeking treatment at health clinics was observed to be very small and many opted to go directly to district or provincial hospitals. A few patients also visited private pharmacies before visiting the health facility (17% in the Lao People’s Democratic Republic). For service quality and provider interaction at the health facility, the majority of the interviewed patients suffering from fever were tested at the facility and half were aware that they were tested for malaria. Regarding patient knowledge and adherence, it was found that most patients were aware of malaria symptoms; however, almost one third patients in both countries had limited knowledge regarding drug resistance. No patients were aware of the malaria treatment received and most treatment courses were completed even after feeling better (88% in the Lao People’s Democratic Republic).

Surveillance activities on quality, source and availability of antimalarial medicines were conducted in the Lao People’s Democratic Republic, Myanmar, Thailand and Viet Nam. A total of 386 samples were collected. The study was approved by the WHO Regional Office for the Western Pacific ethical review committee in August 2016, and sampling took place from December 2016 to March 2017. Testing was completed on 30 June 2017, and the report was released in November 2017. The results are discussed in more detail in Session 5, as presented by United States Pharmacopeia (USP), but in brief; the results demonstrated that of the 386 total samples tested, 117 (30%) were non-conformant.

Finally, a GMS workshop on regulatory actions to counter substandard and falsified medicines was held on 25–27 April 2017 in Bangkok, Thailand. On the first day of the workshop, participants discussed with senior officials cross-border collaboration and aimed to identify key potential regulatory actions needed to eliminate poor-quality antimalarial medicines. On the second day, a hands-on training was conducted on post-market surveillance, inspection and reporting to WHO global surveillance. The meeting recommendation was for WHO to support Member States to
organize bilateral cross-border workshops in provinces along country borders to strengthen regulatory capacity, collaboration and information sharing.

2.2.3 Overview of the Regional Regulatory Partnership

Representatives from the RRP presented key updates. The session was begun by Dr Paul Huleatt, Director, Adverse Event and Medicine Defect Section, Pharmacovigilance and Special Access Branch, Health Products Regulation Group, Australian Government Department of Health. Dr Huleatt presented a number of outcomes from an initial outreach trip held in June 2017 in the Lao People’s Democratic Republic, Cambodia and Thailand. He reported a need to better understand systems, processes and “pain points” and to work within current frameworks in each country, wherever possible. He noted that follow-up trips focused on one country at a time and direct engagement with technical areas should help inform where Therapeutic Goods Administration’s assistance can be focused to have the greatest impact. He then presented key observations from follow-up country visits including that some overlap was found in staff training requirements and some similarities in market authorization processes exists. Each country has distinct challenges including approaches to the development of information technology infrastructure, laboratory infrastructure and capacity, partner activities and the levels of engagement.

Dr Huleatt then discussed the Indo-Pacific Regulatory Strengthening Program, which was launched in October 2017 as a five-year initiative, implemented by the new Indo-Pacific Centre for Health Security at the Australian Government Department of Foreign Affairs and Trade (DFAT). The $300 million investment aims to promote global and regional cooperation, catalyse international responses to national identified needs, apply Australia’s unique strengths in health security and accelerate access to new and effective tools. The programme is centred on building strong working partnerships between the Therapeutic Goods Administration and NRAs to improve regulatory capability and capacity, with a focus on market authorization. Using products related to malaria and tuberculosis as entry points, it will aim to improve regulatory systems to increase the availability of safe and effective essential medicines and medical devices, with a view to support regulatory convergence efforts.

The programme is planned to be implemented over the next four to five years in six countries: the Lao People’s Democratic Republic, Myanmar, Cambodia, Indonesia, Viet Nam and Papua New Guinea, subject to partner government approval. Early engagement with the Lao People’s Democratic Republic and Myanmar has commenced to inform the design, and Dr Huleatt noted that it will be essential to avoid duplication of effort. The programme will be part of the RRP to enhance cooperation and coordination between all partners. Future development plans include ensuring complementarity with other RRP partner activities, coordinating activities and leverage synergies where they are identified; ensuring consistency with RRP work plans (country specific and common activities) and leveraging the detailed regulatory capacity assessments undertaken by the Centre of Regulatory Excellence (CoRE) at the Duke-National University of Singapore (NUS) Medical School.

Next to present was Dr James Leong, Assistant Professor, Head of Pharmaceutical Regulatory Science Programme, CoRE, Duke-NUS Medical School. Dr Leong outlined CoRE’s strategic areas of work including education and training, applied research and policy innovations. The Asian Development Bank–funded CoRE project is a collaboration to promote the availability of safe and effective health commodities within the scope of malaria elimination in the GMS. The project aims to assess the needs and collaborate with stakeholders to strengthen the capacity and capabilities of regulatory agencies in the GMS by implementing relevant, high-quality regulatory training programmes and building sustainable long-term capacity in a realistic manner for more effective regulatory systems. Phase 1 of the project is a needs assessment to clarify capacity and capabilities needs of NRAs and other stakeholders involved in the regulation of medicines and medical devices; Phase 2 is implementation to develop appropriate training programmes identified in Phase 1.
Dr Leong outlined a number of key approaches and products, including a report that reviewed existing information on the regulatory landscape in the GMS; a regulatory systems profiling instrument to identify gaps in the local regulatory systems which referenced the WHO Benchmarking Tool; CoRE teams conducted in-country structured interviews with NRAs and key stakeholders (industry, trade association, pharmacy associations, malaria centres); and identified key gaps and training needs. CoRE has developed country assessment reports and roadmaps for regulatory systems strengthening and held in-country training workshops. From these assessments and reports, CoRE has identified key organizational gaps and key challenges in regulatory functions surrounding medicines and medical devices.

During the discussion, Dr U hjin Kim noted that WHO plans to have training workshops to support post-market surveillance of antimalarial medicines and will work with RRP to coordinate these activities. Dr Mike Ward noted that it is important that each work plan from RRP members should be validated and work with instruments available in each country.

2.3 Session 3: Country updates on national malaria treatment guidelines

2.3.1 Cambodia

Dr Lek Dysoley, Deputy Director, National Center for Entomology, Parasitology and Malaria Control (CNM), presented the Cambodia NTG and implementation status. He noted that multidrug resistance is rampant in Cambodia, which currently has identified four ACTs with high failure rate (>10%). In this situation, the WHO drug policy recommendation is to change ACTs, which was done in 2016-2017. The decision to shift from DHA-PIP to AS-MQ was made with support from WHO after full efficacy was found in 10 TES sites in seven locations since 2009. However, in 2017, two treatment failures of AS-MQ were found (still to be confirmed by PCR). Other ACTs tested for future possible use include AS-AQ (14–23% failures in 2016) and AS-PYR (pyramax) in 2017. A 2016 TES confirmed high DHA-PIP failures in the northeast and continued AS-MQ efficacy.

Dr Dysoley presented details of the NTG for failure identification, referral, second-line treatment and severe malaria cases and referral along with alternative antimalarial medicines. Noteworthy updates to the 2014 guidelines included implementation of single low-dose primaquine for treatment of P. falciparum, included in the 2014 guidelines but not registered until September 2016 and not deployed until August 2017. Additionally a pilot test is being conducted for P. vivax male-only patients (80% of cases are adult males) using Carestart G6PD RDT and radical cure with primaquine in non-deficient cases only (0.25 mg/kg, daily for 14 days). Noted were the limitations of the Carestart G6PD RDT, such as its lacking a control line leading to subjective interpretation, and Global Fund procurement conditions, including defining the limitation of testing for females heterozygous for G6PD deficiency; a plan for ensuring how females that test as non-deficient are provided with appropriate counselling; and an assessment of access to care and capacity of the health services to identify and manage primaquine-induced haemolytic anaemia.

He also presented the contents of an updated NTG training manual, tested in two operational districts, including a complete set of diagnosis and treatment tools, job-aids and posters for health centres, village health workers and private providers. National training of referral guidelines are planned for 2018–2020. Included in the training manual are trainings for case classification with decision algorithm for health facilities and a simplified flow chart for malaria workers. And AS-MQ procurement has been negotiated with the single-source WHO prequalified manufacturer (Cipla) to include required quantification of the fixed dose combination including four age-group blister pack sizes. As for village malaria workers, he reported that 4740 have been trained in 2850 villages and supplied with RDT and ACTs. Private sector malaria services are being provided by 672 providers, supported by Population Services International (PSI) and expansion of 1000 new providers in seven provinces is planned for 2018–2020. A new edition of the Cambodia NTG is planned to be launched in 2018 with minor revisions.
The key issues discussed were the delay to adopt AS-MQ when resistance was found as well as the implementation status of single low dose primaquine to treat *P. falciparum*. The national programme responded that quinine was not given as second line when resistance to DHA-PIP was detected, because patients do not take their full course. Dr Abeyasinghe mentioned that we are dealing with delayed clearance; the maps showed that AS-MQ was used in five provinces in 2014 but distribution was not scaled up nationally even when resistance was determined. He noted that distribution occurred far too slowly for AS-MQ scale-up and full operationalization of single low dose primaquine has taken over three years to adopt. If second line is not used, operationalization of NTGs is not being done correctly. Now there is an opportunity to fully operationalize NTGs, train clinicians, and work on quantification of first- and second-line medicines. Dr Dysoley responded that partners can help to expedite the process, but the challenge remains of training staff and finding the medicine that should be used.

Data in countries are not always robust enough to decide on the clear proportion of cases that fail and need second-line medicine. WHO noted that microscopy is required to confirm failure before giving second-line treatments. An example from Viet Nam was given when the NMP wanted to use AS-MQ but had only TES data for pyramax, meaning that they had to implement based on available data. The Lao People’s Democratic Republic representatives commented that when second-line medicines are used, the number of deaths decreased. Dr Abeyasinghe noted that this is likely because of the partner drug combination, which is able to control the parasite density thereby reducing deaths. But the danger is that parasites that survive become more resistant while the second line becomes less effective.

The role of the Department of Drugs and Foods in Cambodia

Mr Sea Thol, Chief of Essential Drugs Bureau, Department of Drugs and Food (DDF), presented an overview of the DDF and discussed the process for the selection, registration, supply chain of health commodities, the quality monitoring for antimalarial medicines, and challenges and areas for strengthening to ensure access to and availability of quality antimalarial medicines in Cambodia. The DDF consist of five bureaus: registration, essential drug, pharmaceutical trade, drug regulation and food safety. Close collaboration occurs between the DDF and the central medical stores (CMS), which control the distribution and supply of essential medicines, the national health product quality control centre and CNM, which determines antimalarial drug selection and use. Antimalarial medicines are included in the list of essential medicines as listed in the current NTGs, including artemether, 80 mg/ml, artesunate, 60 mg anhydrous artesunic acid, AS-MQ, artesunate rectocap, 50 mg to 200 mg, doxycycline, primaquine 15 mg and quinine, tablets and injectables.

Mr Thol discussed the registration process for antimalarial medicines. Antimalarial medicines are eligible and can be considered for fast-track registration if a formal request is made by CNM. Malaria treatment guidelines are also communicated by CNM to DDF. CNM can make requests for new antimalarial medicines to be registered based on the NTG and levels of parasite resistance determined from TES data. The DDF can withdraw registrations of antimalarial medicines (that is, monotherapy) based on advice provided by CNM, and the DDF is currently revising all guidelines and procedures pertaining to drug registration. The majority of antimalarial commodities are distributed through the national public supply chain system; however, procurement is managed by multiple stakeholders including the ministry of health, UNOPS, and the President’s Malaria Initiative (PMI). In addition to supporting procurement they also support distribution of antimalarials to CMS warehouses. Subnational-level distribution is managed by CMS and provincial health departments. There is a drug inventory database for different distribution and health facility levels; training of health centre staff on drug management; and supervision and monitoring of the availability of essential medicines in health facilities under the Global Fund.

The DDF is responsible for monitoring the quality assurance of antimalarial medicines in public and private sectors. Oral artemisinin monotherapy (oAMT) has been withdrawn since 2009, and there are currently no local manufacturers of oAMTs. In accordance with quality assurance requirements
stipulated by the Global Fund Principle Recipient (UNOPS), the DDF collects ACT samples from the public sector and sends them to an International Organization for Standardization (ISO)-accredited laboratory in Nepal for testing. The DDF also monitors the quality assurance of antimalarial medicines in the private sector by performing inspections in malaria zones and sampling antimalarial medicines. The DDF also supported development of pharmacovigilance guidelines in collaboration with CNM in 2017 and supports implementation of product recall guidelines based on quality control testing and improper labelling.

Challenges identified by DDF include: gaps in collaboration among NRAs in the region; inefficient management of drugs and RDTs, especially at peripheral levels; pharmacovigilance concept is new for consumers and patients; and regulatory system capacity to respond to emerging needs. There is a general lack of capacity in the areas of regulatory knowledge, laboratory analysis performance and pharmacovigilance. Areas to strengthen in Cambodia include the general medicines regulation system (capacity-building and hardware), health products vigilance, staff training and supply chain practices. Cambodia must also link adverse event reporting systems to other electronic health-care systems to make submission of adverse event reports easier and coordinated.

2.3.2 The Lao People’s Democratic Republic

The Lao People’s Democratic Republic presented the history and current status of its NTG, malaria surveillance issues and TES results in 2016–2017. From 2005 to 2015, the first-line treatment for *P. falciparum* and *P. vivax* was AL, which changed to AL and single low-dose primaquine in 2015 and remains in place today. AL plus primaquine (14 days) with G6PD testing is the current treatment policy for *P. vivax*. In 2018, testing and treatment by health centres and village health volunteers was authorized. TES results from 2016–2017 demonstrated 50% clinical response to DHA-PIP and >80% clinical response to AL.

In the Lao People’s Democratic Republic, the antimalarial drug supply in the private sector must be registered according to Ministry of Health Regulation 1820, dated 25 August 2017. The drug supply for the NMP is donated by the project and conforms to the NTGs. Current NTG implementation challenges include: testing for G6PD deficiency with prequalified products; monitoring primaquine 14-day compliance; prescribing primaquine at community facilities and functionality of the referral system for radical treatment of all *P. vivax* cases at health centres and hospitals; the risk of further spread of multidrug resistance; and sustainability of newly developed quality assurance protocols for malaria diagnosis.

The NMP plans to include TES in two southern provinces in 2018 to test AS-MQ and AS-PYR efficacy for both falciparum and vivax malaria; single low-dose primaquine treatment for all *P. falciparum* cases in all provinces and service delivery areas; training at all service levels on the new NTGs, including revised job aids; and establishment of new diagnostic quality assurance protocols. An issue was raised during the discussion about antimalarial drugs that were previously registered but expired and not being imported into the country. The programme noted that each drug must still have a waiver to import, even if previously registered.

2.3.3 Viet Nam

Dr Bui Quang Phuc of the National Institute of Malariology, Parasitology, and Entomology (NIMPE) presented updates on the implementation status of its NTGs, key antimalarial medicines for resistant foci and current implementation challenges. TES results of DHA-PIP in 2016 demonstrated the following clinical efficacies: Dak Nong (73%); Dak Lak (100%); Bin Phuoc (54%); and Khanh Hoa (96%). In 2017, TES was done for pyramax in five provinces: Dak Nong, Gia Lao, Ninh Thuan, Khanh Hoa and Binh Phuoc, testing a total of 236 patients. Adequate clinical parasitological response was found to be 96% with Day 3 positivity of 26%. Provinces with the lowest clinical response were Binh Phuoc (94%) and Dak Nong (83%). In 2018, the programme will continue TES of pyramax, begin TES for AS-MQ and plan for iDES. The Viet Nam NTGs were updated in 2016 to include
AS-MQ or pyramax for uncomplicated falciparum malaria in addition to the established DHA-PIP plus primaquine. A number of challenges for implementing the NTGs were noted, including the non-availability of alternative antimalarial drugs for areas of artemisinin resistance; the need for G6PD RDTs; poor compliance for primaquine treatment in *P. vivax* patients; and lack of information from private sector.

Dr Hoang Thanh Mai of the Drug Administration of Viet Nam (DAV) presented the health products management system and issues on drug regulation. The DAV functions to develop policies and legal documents and to manage drug registration and marketing authorization. It also creates proposals to the Ministry of Health for making decisions on clinical trial of drugs to be registered or imported to Viet Nam, manages drug marketing and pharmaceutical practices and drug quality management, as well as drug information and advertising, pharmacovigilance, rational and safe use of drugs. The DAV also sets drug price and drug bidding management issues; traditional and herbal drugs; participates as the focal point in provision of direction, implementation of adequate drug supply for the hospitals; and provides technical direction and conducts inspection. The Drug Registration Division provides marketing authorization and ensures drug quality and efficacy of drugs, including antimalarial medicines.

Dr Mai discussed the general requirements of drug registration. Dossiers are written in English or Vietnamese languages, while package inserts and summary of product labels are in Vietnamese. Certificate of analysis maintains compliance with international standards and clinical trials are only required for new drugs. Dr Mai outlined the process of new drug applications and how drugs qualify for priority review, including locally manufactured in GMP compliant facilities and ad-hoc treatments on a list of orphan drugs or needed for emergencies, disasters or epidemics. Drug approval times vary depending on first time registration (12 months), minor variations (60 days) or notification only (20 days). Once registered, drugs are valid for a maximum of five years. Although Viet Nam allows a fast-track approval for WHO prequalified vaccines, this fast track does not apply for medicines, including ACTs.

### 2.4 Session 4: Improving access to antimalarials for accelerated malaria elimination

#### 2.4.1 Access framework and its application for antimalarials

Dr Paul Lalvani, WHO Temporary Advisor, presented a framework on access to antimalarial medicines. The framework included five components: availability, affordability, acceptability, appropriate quality and rational use. Dr Lalvani discussed in detail each component that is needed to ensure access to antimalarial medicines. The details for each component are listed below.

- **Availability**: globally (manufacturers, exporters, international wholesalers); nationally (policy- ministries of health, NTG, essential medicine list, regulatory, procurement); point of care (supply chain, proximity to health-care facilities).
- **Affordability**: globally (donor funding, manufacturer pricing); nationally (budget for medicines, diagnostics); point of care (total cost to patient, product, travel, wages lost).
- **Acceptability**: globally (WHO policy, donor policy); nationally (NTG, EML, advocacy, social marketing); point of care (use of ACTs only after testing, such as the use of Primaquine).
- **Appropriate quality**: globally (WHO prequalification, United States Food and Drug Administration, European Union Article 58); export country standards; import country national standards; point of care supply chain quality (good storage practice, good distribution practice especially for heat sensitive products, counterfeit products).
- **Rationally used**: globally (share best practice); nationally (policy, capacity building of health centre staff and advocacy for patients); point of care (patient and caregiver advocacy, human resources, health system, village health worker).
Dr Lalvani emphasized the two components, availability and appropriate quality. He noted that WHO can use the framework to map out and understand the steps needed to improve access, and work with NMPs and NRAs to better support countries to define roles and responsibilities.

2.4.2 Establishing a virtual stockpile of antimalarials to expedite access and availability of ACTs

Dr Soso Getsadze, Specialist, Health Products Management, Global Fund, presented the Global Fund Rapid Supply Mechanism (RSM) that was established to provide emergency stocks of antimalarial medicines to countries. The RSM was developed to reduce procurement lead time, increase availability of medicines, respond to stock-outs and respond to changes in treatment regimens. It is available for all Global Fund Principal Recipients. The approach of the RSM includes a vendor-managed inventory whereby the Global Fund has agreements with selected suppliers to manage a rotating stock of key WHO recommended antimalarial medicines. Key products with formal agreements in place include AL, artesunate/amodiaquine and artesunate injectables. AS-MQ, primaquine and atovaquone/proguanil are not yet available but are being added to the list of products available through the RSM. Target time frame for delivery of medicines is 4–6 weeks from request to arrival. The ordering process is streamlined to include a single RSM form, completed and signed, and funds should be available and order confirmed by the Principal Recipient.

The discussions began with the issue of quantification. One of the reasons the Global Fund developed the RSM was due to countries needing to order small quantities of medicines for outbreak situations or foci of resistance. But it was also noted that there is currently a need to better specify and quantify antimalarial medicines needed to prevent urgent request orders. As part of the RSM process, drug stocks are rotated at manufacturer level and as such, these companies share the risk of loss. Management of stocks are at the national level. It was noted that national funds, apart from Global Fund monies, could not be used to procure antimalarial medicines via the RSM and that there are currently no limits on the amount of antimalarials that can be procured via the RSM. Prices are negotiated with manufacturers and 5% cost added to all orders.

Dr Abeyasinghe noted that the RSM is a contingency mechanism and should not be used to replace the national supply management system. It was established to deal with unforeseen resistance or outbreak situations and should only be used to ensure supplies are available in emergency or short term situations where smaller quantities are required. Dr Ringwald noted that the primary problem in the GMS has been an inability for countries to access AS-MQ, as seen in Cambodia. The Global Fund replied that a solution is being developed: a batch order has been placed for Cambodia, Viet Nam and countries in the Pan-American Health Organization, plus the remaining for use via RSM orders. This batch order is being done along with Global Fund planning for next AS-MQ batch order.

The process was discussed for ordering antimalarial medicines using the RSM when drugs were not included as part of nationally registered products. Countries must first quantify needs and prepare import registrations prior to accessing the RSM. It is important that NMPs expand TES for all ACTs in all countries, unless ACT failed previously. An assessment should be done to identify which TES sites to include what products for access to new ACTs. Emergency supply management teams should update and facilitate the process of accessing the antimalarial medicines on the list. Together with the regulatory bodies, national and international, NMPs need to look for exceptions and options or waivers to access and utilize these drugs.

2.4.4 Registration pathways for accelerating marketing authorization of antimalarials

Dr Mike Ward presented on accelerating registration of antimalarial medicines. A variety of instruments are available to facilitate registration of quality-assured products, including the WHO prequalified collaborative registration procedure for prequalified products; facilitated registration procedure of SRA approved medicines; ASEAN Joint Assessment Process and European Union Article 58, Swiss marketing authorization for global health products (MAGHP). The WHO prequalified collaborative registration procedure has been developed to enhance timely access to
prequalified products and to ensure that products in countries are the same as prequalified products. The procedure was first piloted in June 2012; it also benefits manufacturers of prequalified products through faster and better harmonized regulatory approvals in participating countries.

The steps in the collaborative procedure involve an agreement and the registration process. As for the agreement, an NRA confirms to WHO its interest to participate in collaborative procedure and to respect its conditions. Focal persons are designated at each interested NRA, sign confidentiality agreements and are given access to the WHO managed restricted access platform. For registration, a manufacturer submits an application to participating NRAs for the prequalified product and informs the authority about the interest to follow the collaborative procedure. The manufacturer informs the WHO team about the application for national registration and, for each product, provides written agreement to exchange of information between the participating NRA and WHO.

Next, the participating authority confirms to WHO its interest to apply the procedure for a given product and within 30 days, WHO provides a focal person in the participating NRA with assessment and inspection reports via restricted-access website (MedNet). Within 90 days, the participating NRA decides upon the national registration, informs WHO about the outcome of national registration and, when divergent from a WHO decision, provides explanations. Within 30 days of having taken its decision, the participating NRA informs WHO and the applicant of the decision. WHO lists products registered by participating NRAs on its public website. As of September 2017, the Lao People’s Democratic Republic and Thailand are the only countries in the GMS that have participating NRAs.

Dr Ward also presented the collaborative procedure in the assessment and accelerated national registration of pharmaceutical products approved by Stringent Regulatory Authorities (Collaborative Registration Pilot). A primary concept of the SRA is zero duplication of effort. The principal roles of the WHO to assist in the execution and maintenance of the procedure, posts lists of participating NRAs and SRAs on its website and collects information about performance of the procedure. Also, WHO actively facilitates information exchange among involved SRAs and participating NRAs when medicines are therapeutically relevant for WHO supported treatment programmes. As of November 2017, no countries in the GMS are participating in the pilot SRA procedure. Regulators in the WHO Western Pacific and South-East Asia Regions are not taking advantage of opportunities to facilitate registration, build capacity and make better use of limited resources. Dr Ward suggested countries take advantage of these resources. WHO is available to assist countries in the use of facilitated registration pathways, including SRA approvals.

The Lao People’s Democratic Republic joined the prequalification registration procedure but signed a confidentiality agreement regarding accessing documents and products. Representatives from the Lao People’s Democratic Republic noted that their experience in dealing with required documents is they are time consuming and complex. UNOPS suggested that WHO assist countries through a collaborative process to expedite waivers to use needed drugs immediately. Dr Ward responded that WHO has done much work concerning drug emergencies and is now prioritizing diseases and developing platforms.

Regarding regulatory access, outcomes have included recommendations to WHO to provide guidance on what regulatory frameworks can be included (that is, critical instrument frameworks). During emergencies, instruments typically do not exist but as part of WHO normative work, guidance can be developed. Conversations with countries need to be confidential to determine options to solve some of these challenges. It was also noted that in areas with low malaria transmission, there is no market incentive to register products as manufactures are not sufficiently incentivized. Dr Ward responded that as with neglected tropical diseases, registrations will be warranted by countries, or if not, perhaps through donations. Registration is an issue but where opportunities exist, they can be taken advantage of. CoRE raised the issue of the process for maintenance and update to the procedure when manufactures with low volumes, following a single dossier method, have variations in requirements. Dr Ward replied that a local agent is needed. Harmonization of requirement is the best approach and
this approach is being taken by ASEAN. Prequalification identifies variances and manufactures should file changes, as done initially.

2.4.5 Procurement and supply chain framework and steps for improving availability of antimalarials

Dr Paul Lalvani presented a framework for procurement and supply optimization. He identified components of the framework, including policy, process and supporting functions and systems. The policy component consisted of strategies, guidelines and manuals, while the processes included product selection, forecasting procedures, procurement, inventory management, distribution and ensuring rational use. The supporting functions and systems component included data management, financial management, human resources management, coordination, risk management, quality management and communication strategies. Dr Lalvani outlined the process for new product development, introduction and rational use. The following list includes the key steps and descriptions.

- **Product development**: new product developed by manufacturer (often with Product Development Partnerships).
- **National treatment guidelines**: WHO assesses the benefit of the product and may provide recommendations; countries/public health programmes may consider including this in their NTGs at national or subnational levels.
- **Quality and registration**: manufacturer may submit the product for WHO prequalification, and/or submit for registration in various markets; WHO reviews; Country NRA registers product or provides a waiver for importation/use.
- **Funding**: donors may fund the purchase and donation of the product (usually based on WHO recommendations); countries may choose to fund the medicine through their own budget.
- **Procurement process**: countries engage in product selection; conduct forecasting and quantification exercises; place orders for purchase of medicines; manufacturer produces the medicines and supplies directly or through intermediary mechanisms (exporter, international wholesaler, Global Fund mechanism).
- **Storage**: port clearance and moving of goods to storage facilities; ensure there is sufficient storage capacity at national and subnational levels; ensure quality and quantity of storage facilities/infrastructure; ensure proximity of storage to point of care; if there are gaps, explore short- and longer-term solutions (such as facilities, contract partners, private sector).
- **Distribution**: identify quality-assured transporters of medicines; contract these transporters; ensure regular supply using pull or push mechanism.
- **Rational use**: ensure all health workers know policies, procedures, standard procedures for prevention, testing and treatment; engage in continuous and dispersed training at scale of all health-care staff; conduct advocacy for consumers to promote.
- **Quality assurance**: ensure quality assurance is part of the entire process at time of procurement, contracting, shipping, storage, distribution, dispensing.
- **Surveillance**: test for resistance, delayed clearance, new cases; review and adapt guidelines for treatment and procurement.

2.5 Session 5: Quality of antimalarials in the GMS

2.5.1 Results of antimalarial quality survey in four GMS countries

Dr Souly Phanouvong, Director of Global Public Health Asia, USP, presented the objectives, methods, results and conclusions of the random sampling survey of antimalarial medicine quality in four GMS countries. The objectives of the survey were to: determine the prevalence of good-quality (and poor-quality) antimalarial medicines being produced, supplied, and circulated to the public, private and other sectors in selected areas, mainly along national borders where resistant malaria has been reported; understand the availability of antimalarial medicines (with focus on ACT and oAMT) and their sources; identify areas of problems with poor-quality antimalarial medicines that require greater investments and interventions; and propose pragmatic recommendations for interventions to better
support national and regional malaria elimination strategies. The survey conceptualization phase was in September 2016; the sample testing, data collection and analysis phases were in October 2017; and sharing of results in 2018.

The study was a descriptive, cross-sectoral survey with random sampling methodology. Of the 565 samples collected, 386 were tested using pharmacopoeial procedures and specifications. Of the 386 samples tested, 72% (n = 278) were registered. Samples were collected in a number of provinces in the Lao People’s Democratic Republic, Thailand, Viet Nam and Myanmar. Thirteen unique antimalarial products were collected for sampling and testing. Samples were tested at the USP India Laboratory, an ISO 17025-accredited laboratory. All critical tests using the cut-off protocol in the compendial monograph of the most-recent pharmacopoeias were conducted (United States, United Kingdom and International pharmacopoeias).

The combined results from all four countries demonstrated 70% (n = 269) conformant samples and 30% (n = 117) non-conformant samples. Of the 49 non-registered samples tested, 82% (n = 40) were conformant. Some reasons for non-conformance were presented, including low levels of active pharmaceutical ingredients (APIs), low levels of dissolution properties and impurities. Dr Phanouvong highlighted oAMT findings. Even though all GMS countries have issued a national policy to ban oAMT, 12 oAMT samples were found during the survey. The oAMT availability reflects the policy and regulatory non-alignment between regulatory agencies and programmes as well as the pharmaceutical industry. Evidence suggests that oAMTs not only are still produced in some countries and used in most GMS countries, but also are of “bad quality”.

The key observations discussed included the quality of antimalarial medicines as a national public health threat and an inadequate registration system troubled with limited capacity in post-marketing surveillance. The study findings suggest that current registration systems need improvement. The same product lot number failed quality testing throughout its supply chain, that is, from public provincial warehouse and hospital to district health centres. As such, substandard quality antimalarial medicines are being used in the public sector and sold in the private market. Some recommended solutions included regulatory system strengthening and stakeholder engagements as well as increased bilateral and regional cooperation in border control and inspections. For both prophylaxis and malaria case management, it is critical that medicines are safe and of assured quality. Efforts to eliminate substandard and falsified antimalarial medicines must be intensified and sustained. Otherwise these products would contribute to treatment failure, long hospital admission, and may lead to increased resistant malaria which would result in negative economic implications on both the government and individuals.

An engaging discussion followed the presentation. Thailand noted that the criteria for determining non-conformance suggested that the issue of substandard medicines is not true for Thailand. USP responded that leading pharmacopeia standards, not just national criteria, must be used during the classification of substandard status. One option suggested was to test the samples collected using the standard in Thailand. CoRE asked if the poor conformance results were due to poor manufacturing practices or poor distribution and storage practices and if registration does not guarantee quality, how can the situation be improved. USP responded that most countries do not test samples when initially imported upon registration and encouraged countries to use retention samples to test and assess quality. Registration is meeting requirements to bring product to market but not assessing the product quality over time. Viet Nam questioned the results and why they were different to country results. USP responded again that they used the leading pharmacopoeias for testing these products but if these are not available, they would use national pharmacopoeia.

Dr Abeyasinghe noted that the results indicated that active ingredients and solubility were not up to standard (meaning active ingredients are not effective against parasites) and asked if similar results were found in country by NRAs and what is done in countries. Viet Nam noted that it conducts TES to determine if drugs are effective or not in patients. It was noted that for TES, registered products are used but in the field, some drugs are used that are not tested in TES. Dr Abeyasinghe emphasized that
NMPs need to strengthen supply management systems together with partners, including NRAs, to address this issue and NRAs need to support NMPs to improve the outcome of this problem. Dr Ward stated that regulatory authorities must take action and further investigate these results.

2.5.2 Market surveillance, control and vigilance

Dr Mike Ward presented a holistic, targeted regulatory support based strategy on three inter-related areas: registration/market authorization, vigilance, and market surveillance and control. The strategy is a phased approach divided into short (less than two years), medium (two to five years) and longer term (more than five years) interventions, considered based on potential for greatest impact to promote malaria elimination. Coordination of partner technical assistance and capacity-building efforts through the CIP, based on pre-agreed roles and country and regional work plans are required, as well as leveraging existing regional regulatory networks.

Dr Ward discussed the role of WHO in market surveillance and control, including protection of public health, political support, improving access to safe effective medicines, and ensuring collaboration and coordination. For vigilance, there are three main challenges: limited reporting; low capacity to analyse data collected; and low NRA capacity to take action from alert signals received. Only a small fraction (3 in 55 according to 2010 survey by WHO) of the NRAs regularly take specific actions from signals. He then discussed proposed actions in which national programmes should establish regional sentinel sites and commence post market surveillance on the medicines most at risk. Methods should include sampling, laboratory analysis and reporting, and survey protocols, including testing methodologies based on WHO guidelines and utilizing newly developed definitions of medical products. Programmes need to establish sentinel site locations to be identified in urban and rural areas, border and non-border locations, and include public and private outlets.

2.5.3 Global Fund RA12E pharmaceutical activities

Dr Uijn Kim outlined the proposed pharmaceutical component activities under the Global Fund grant, Package 3: Ensuring availability of quality health commodities across the GMS. The goal of the grant is to ensure improved access to quality-assured and appropriate combination antimalarial products and to ensure their appropriate use in all GMS countries. The specific objectives are to strengthen regulatory capacity, to ensure availability of quality-assured products in both public and private sectors, and to eliminate substandard, falsified products from the subregional market.

She proposed that two to three countries in the GMS work with WHO and other partners to develop national plans on prevention, detection and response to substandard and falsified products and to support strengthening regulatory capacity across hotspot border areas, including Myanmar–China and Myanmar–Thailand in 2018 and Thailand–Lao–Cambodia and Viet Nam–Lao in 2019. A third activity to be conducted is to raise public awareness on oAMT and drug resistance.

2.2.5 Closing remarks

Dr Rabindra Abeyasinghe gave the closing remarks. He thanked everyone for joining this important meeting in Phnom Penh to review and discuss NTGs, and how to improve and expedite access to essential antimalarial medicines, which will be a key factor in accelerating malaria elimination in the GMS.
3. CONCLUSIONS AND RECOMMENDATIONS

3.1 Conclusions

Countries of the GMS have made considerable progress towards updating their NTGs and have done considerably well in preventing the emergence of new foci of resistance since 2015.

Updated NTGs are not fully operationalized in most GMS countries, particularly related to the availability and use of second-line treatments for uncomplicated malaria, and with implementation of primaquine regimes for all forms of malaria.

Only first-line ACTs are registered in most GMS countries, resulting in significant delays in accessing second-line or alternative ACTs, particularly for treatment in foci of resistance.

In some instances, significant delays implementing NTGs (first-line treatments) after resistance was detected likely contributed to exposing resistance parasite to suboptimal ACTs for prolonged periods, possibly leading to greater resistance levels in parasite populations (though not associated with increased mortality).

Countries of the GMS have continued to strengthen TES for antimalarial medicines; however, ACTs being subjected to TES are limited, which restricts the ability of countries to make informed choices regarding changing first-line treatments when faced with resistance.

Quantification of antimalarial medicines in most GMS countries is determined based on historical epidemiological data rather than current transmission dynamics, resulting in treatment supply management challenges and often resulting in a need for antimalarial medicine redistribution at the periphery.

The Global Fund has established a RSM to provide grant recipient countries rapid access to antimalarial medicines when faced with stock outs or resistance, however, national drug registration and national regulation still needs to be addressed for countries to effectively make use of the RSM.

Some WHO prequalified or registered antimalarial medicines in the GMS have tested non-conformant to international standards in post-market quality testing. However, pre-shipment testing was not conducted on most of the antimalarial medicines subject to post marketing testing and hence it's difficult to determine if substandard products were due to manufacturing issues or degradation along the supply chain. Follow up investigation is recommended.

National regulatory authority capacity and regional regulatory partnership mechanisms are not adequately supported or funded in most GMS countries resulting in an inability for countries to accelerate the introduction of appropriate antimalarial medicines.

3.2 Recommendations

3.2.1 Recommendations for Member States

Member States are encouraged to do the following:

1) Update NTGs based on the latest TES results and expedite full operationalization of revised treatment guidelines for first- and second-line therapies and primaquine regimes for all forms of malaria, including development of necessary bench aids and clinician trainings.

2) Expand TES in all Western Pacific Region GMS countries to include currently available, effective ACTs.

3) Acknowledging problems associated with accessing small quantities of new ACTs, countries are encouraged to access such requirements through the RSM established by the Global Fund;
however, the RSM should not be viewed as a solution for inadequate procurement and supply management planning processes.

4) National malaria control programme staff and supply management staff are encouraged to work closely together and use strengthened surveillance data to more accurately quantify and distribute antimalarial medicines, including ACTs.

5) Accelerate efforts to strengthen core regulatory functions by: (a) adopting mechanisms to accelerate the registration of priority treatments (all ACTs) and diagnostics, including through WHO collaborative procedures and SRA-facilitated registration; and (b) strengthening post-market and vigilance functions to ensure access to safe and quality-assured antimalarial medicines.

3.2.2 Recommendations for the Secretariat

The Secretariat is requested to do the following:

1) Support national malaria control programmes to update their NTGs and to fully operationalize said guidelines, including primaquine treatment for all forms of malaria.

2) Support country expansion of TES to include all currently effective ACTs and support field testing of iDES in select areas of low malaria transmission.

3) Support implementation of needs-based access to the Global Fund's RSM and support countries to address regulatory constraints restricting rapid access to antimalarial medicines through RSM.

4) Support the identification of procurement bottlenecks for WHO prequalified or registered products while encouraging pre-shipment and post-marketing quality testing.

5) Encourage strengthening of quantification for treatment supply management; support malaria epidemiological surveillance strengthening to better quantify antimalarial medicine requirements based on transmission dynamics rather than historical data.

6) Support strengthening of regulatory authorities to register all available ACTs and to expand pharmacovigilance and quality assurance of antimalarial medicines.

7) Encourage investments to strengthen national regulatory authority capacity and regional regulatory partnership mechanisms.

8) Promote coordinated, prioritized support to regulatory system strengthening in conjunction with other technical partners, in particular to expedite access to antimalarial medicines and new products for malaria control.
## Timetable

### Day 1: Monday, 26 February 2018

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
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<tbody>
<tr>
<td>08:30 – 09:00</td>
<td>Registration</td>
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<tr>
<td>09:00 – 09:30</td>
<td><strong>Opening Session</strong></td>
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<td></td>
<td>Welcome remarks Dr Yunguo Liu, WR Cambodia</td>
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<td></td>
<td>Meeting objectives and expected outcomes Dr Rabindra Abeyasinghe, Coordinator, Malaria, other Vectorborne and Parasitic Diseases (MVP), WPRO</td>
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<td></td>
<td>Self-introduction of participants and observers</td>
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<td></td>
<td>Nomination of the Chair and Rapporteur Dr Hiromasa Okayasu, Coordinator, Mekong Malaria Elimination Hub</td>
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<tr>
<td>09:30 – 10:00</td>
<td>Group photograph followed by coffee/tea break</td>
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<tr>
<td>10:00 – 10:30</td>
<td>Session 1: Overview of global and regional malaria treatment guidelines</td>
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<td></td>
<td>Updates on artemisinin resistance and guidance for the current WHO treatment policies including treatment options in foci of resistance in the GMS Dr Pascal Ringwald, Coordinator, Drug and Efficacy Response (DER), Global Malaria Programme (GMP), WHO HQ</td>
</tr>
<tr>
<td>10:30 – 10:50</td>
<td>Overview of current malaria situation in GMS WPR countries: Cambodia, the Lao People’s Democratic Republic and Viet Nam Dr Hiromasa Okayasu, Coordinator, MME</td>
</tr>
<tr>
<td>10:50 – 11:10</td>
<td>Current national treatment guidelines in GMS WPR countries: Cambodia, the Lao People’s Democratic Republic and Viet Nam Dr Rabindra Abeyasinghe, MVP/WPRO</td>
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<tr>
<td>11:10 – 11:30</td>
<td>Discussion</td>
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<tr>
<td>11:30 – 11:45</td>
<td>Session 2: Regulatory frameworks for elimination settings: progress to date</td>
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<td>Update on Coalition of WHO and Interested Partners Supporting Regulatory Systems Strengthening and its work in the GMS Dr Mike Ward, Coordinator, Regulatory Systems Strengthening (RSS), Essential Medicines and Health Products (EMP), WHO HQ</td>
</tr>
<tr>
<td>11:45-12:00</td>
<td>Update on pharmaceutical system strengthening work in the GMS Ms Uhjin Kim, Technical Officer, Essential Medicines and Health Technologies (EMT), WPRO</td>
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<tr>
<td>12:00-13:00</td>
<td>Overview of the Regional Regulatory Partnership Contributions of RRP partners APLMA secretariat TGA CoRE DFAT</td>
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<td>Discussion</td>
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<tr>
<td>13:00 – 14:00</td>
<td>Lunch break</td>
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<tr>
<td>14:00 – 14:45</td>
<td>Session 3: Country updates on national malaria treatment guidelines</td>
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<td></td>
<td>Cambodia: update on implementation status of national treatment guidelines, key antimalarial medicines for resistant foci and current implementation challenges Cambodia</td>
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<td>Discussion (15 min)</td>
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<td>Time</td>
<td>Session Details</td>
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<tr>
<td>14:45 – 15:30</td>
<td>The Lao People’s Democratic Republic: update on implementation status of national treatment guidelines, key antimalarial medicines for resistant foci and current implementation challenges</td>
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<td><strong>Discussion (15 mins)</strong></td>
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<tr>
<td>15:30 – 15:45</td>
<td>Coffee / tea break</td>
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<tr>
<td>15:45 – 16:30</td>
<td>Viet Nam: update on implementation status of national treatment guidelines, key antimalarial medicines for resistant foci and current implementation challenges</td>
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<td><strong>Discussion (15 mins)</strong></td>
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<tr>
<td>18:00 – 19:30</td>
<td>Welcome reception</td>
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**Day 2: Tuesday, 27 February 2018**

**Session 4:** *Improving access to antimalarial medicines for accelerated malaria elimination*

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
<th>Speaker/institution</th>
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<tbody>
<tr>
<td>09:00 – 09:15</td>
<td>Access framework and its application for antimalarials</td>
<td>Dr Paul Lalvani, WHO temporary advisor</td>
</tr>
<tr>
<td>09:15 – 09:45</td>
<td>Establishing a virtual stockpile of antimalarials for GMS countries to expedite access and availability of ACTs</td>
<td>Dr Soso Getsadze, Specialist, Health Products Management, Global Fund</td>
</tr>
<tr>
<td>09:45 – 10:10</td>
<td>The need for flexibility in accessing new ACTs, quantifying the need and accessing a virtual stockpile from Global Fund</td>
<td>Dr Rabindra Abeyasinghe, Dr Soso Getsadze</td>
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<tr>
<td>10:10 – 10:30</td>
<td><strong>Discussions</strong></td>
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<td>10:30 – 11:00</td>
<td>Coffee/tea break</td>
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<tr>
<td>11:00 – 11:30</td>
<td>Recap on registration pathways for accelerating marketing authorization of antimalarials in the GMS</td>
<td>Dr Mike Ward,</td>
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<tr>
<td>11:30 – 12:00</td>
<td>Procurement and supply chain framework and key steps for improving availability of antimalarials</td>
<td>Dr Paul Lalvani</td>
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<tr>
<td>12:00 – 12:30</td>
<td><strong>Discussions</strong></td>
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<tr>
<td>12:30 – 13:30</td>
<td>Lunch break</td>
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<tr>
<td>13:30 – 14:30</td>
<td><em>Country exercise for regulatory strategy and steps</em></td>
<td>Dr Mike Ward</td>
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<tr>
<td>14:30 – 15:30</td>
<td><em>Country exercise for PSM</em></td>
<td>Dr Paul Lalvani</td>
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<tr>
<td>15:30 – 16:00</td>
<td>Coffee/tea break</td>
<td>Cambodia, The Lao People’s Democratic Republic, Viet Nam</td>
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<tr>
<td>16:00 – 17:00</td>
<td>Report back by countries</td>
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**Day 3: Wednesday, 28 February 2018**

**Session 5:** *Quality of antimalarial medicines in the GMS*

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<tr>
<th>Time</th>
<th>Activity</th>
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<tbody>
<tr>
<td>09:00 – 10:15</td>
<td>Results of antimalarial quality survey in 4 GMS countries</td>
<td>Dr Souly Phanouvong, Director, Global Public Health – Asia, USP</td>
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<td><strong>Discussions</strong></td>
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<tr>
<td>10:15 – 10:40</td>
<td>Market surveillance, control and vigilance</td>
<td>Dr Mike Ward</td>
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<td><strong>Discussions</strong></td>
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<td>10:40 – 11:00</td>
<td>Coffee/tea break</td>
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<td>Time</td>
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<tr>
<td>11:00 – 11:30</td>
<td>Update on implementation status of national treatment guidelines, key antimalarial medicines for resistant foci and current implementation challenges</td>
<td>Myanmar</td>
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<td>Discussions</td>
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<tr>
<td>11:30 – 12:00</td>
<td>Update on implementation status of national treatment guidelines, key antimalarial medicines for resistant foci and current implementation challenges</td>
<td>Thailand</td>
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<td>Discussion</td>
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<td>12:00 – 13:00</td>
<td>Lunch break</td>
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<tr>
<td>13:00 – 13:30</td>
<td>RRP common activities and workplan</td>
<td>Dr Mike Ward</td>
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<td>Dr Geoff Clark, APLMA</td>
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<td>13:30 – 14:30</td>
<td>Global Fund RAI 2 Pharma activities</td>
<td>Ms Uhjin Kim</td>
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<td>Discussions</td>
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<td></td>
<td><strong>Conclusions and closing</strong></td>
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<tr>
<td>14:30 – 15:30</td>
<td>Conclusions and recommendations</td>
<td>Dr Rabindra Abeyasinghe</td>
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<td></td>
<td>Closing remarks and next steps</td>
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<td>15:30 – 15:45</td>
<td>Coffee/tea break</td>
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</table>
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