THE SIXTH MEETING OF THE GREATER MEKONG SUBREGION (GMS) THERAPEUTIC EFFICACY STUDIES (TES) NETWORK

27–28 September 2018
Luang Prabang, Lao People’s Democratic Republic
WORLD HEALTH ORGANIZATION
REGIONAL OFFICE FOR THE WESTERN PACIFIC

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MEETING REPORT

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Convened by:

WORLD HEALTH ORGANIZATION
REGIONAL OFFICE FOR THE WESTERN PACIFIC

Luang Prabang, Lao People’s Democratic Republic
27–28 September 2018

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NOTE

The views expressed in this report are those of the participants of the Sixth Meeting of the Greater Mekong Subregion (GMS) Therapeutic Efficacy Studies (TES) Network and do not necessarily reflect the policies of the conveners.

This report has been 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 Sixth Meeting of the Greater Mekong Subregion (GMS) Therapeutic Efficacy Studies (TES) Network in Luang Prabang, Lao People’s Democratic Republic from 27 to 28 September 2018.
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**Keywords:**
Drug resistance / Malaria / Regional health planning / Asia, Southeastern
<table>
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<tr>
<th>Abbreviation</th>
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<tbody>
<tr>
<td>ACPR</td>
<td>adequate clinical and parasitological response</td>
</tr>
<tr>
<td>ACT</td>
<td>artemisinin-based combination therapy</td>
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<tr>
<td>AL</td>
<td>artemether + lumefantrine</td>
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<tr>
<td>AM</td>
<td>artemether</td>
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<tr>
<td>AS</td>
<td>artesunate</td>
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<tr>
<td>ASAQ</td>
<td>artesunate + amodiaquine</td>
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<tr>
<td>ASMQ</td>
<td>artesunate + mefloquine</td>
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<tr>
<td>ASPY</td>
<td>artesunate + pyronaridine</td>
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<tr>
<td>BVBD</td>
<td>Bureau of Vector Borne Diseases</td>
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<tr>
<td>CMPE</td>
<td>Centre for Malaria, Parasitology and Entomology</td>
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<tr>
<td>CQ</td>
<td>chloroquine</td>
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<tr>
<td>DBS</td>
<td>dried blood spots</td>
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<tr>
<td>DHA-PPQ</td>
<td>dihydroartemisinin + piperaquine</td>
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<tr>
<td>G6PD</td>
<td>glucose-6-phosphate dehydrogenase</td>
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<tr>
<td>GMS</td>
<td>Greater Mekong Subregion</td>
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<tr>
<td>iDES</td>
<td>integrated drug efficacy surveillance</td>
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<tr>
<td>IPC</td>
<td>Institut Pasteur du Cambodge</td>
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<tr>
<td>K13</td>
<td>Kelch 13</td>
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<td>MME</td>
<td>Mekong Malaria Elimination</td>
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<tr>
<td>MQ</td>
<td>mefloquine</td>
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<td>NTG</td>
<td>National Treatment Guidelines</td>
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<tr>
<td>PCR</td>
<td>polymerase chain reaction</td>
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<tr>
<td>Pf</td>
<td><em>Plasmodium falciparum</em></td>
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<tr>
<td>Pfpm2-3</td>
<td>Pf plasmepsin 2-3</td>
</tr>
<tr>
<td>PPQ</td>
<td>piperaquine</td>
</tr>
<tr>
<td>PQ</td>
<td>primaquine</td>
</tr>
<tr>
<td>Pv</td>
<td><em>Plasmodium vivax</em></td>
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<tr>
<td>PYR</td>
<td>pyronaridine tetraphosphate</td>
</tr>
<tr>
<td>QA</td>
<td>quality assurance</td>
</tr>
<tr>
<td>QC</td>
<td>quality control</td>
</tr>
<tr>
<td>RDT</td>
<td>rapid diagnostic test</td>
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<tr>
<td>TES</td>
<td>therapeutic efficacy studies</td>
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<td>WHO</td>
<td>World Health Organization</td>
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The Sixth Meeting of the Greater Mekong Subregion (GMS) Therapeutic Efficacy Studies (TES) Network was convened in Luang Prabang, Lao People’s Democratic Republic, from 27 to 28 September 2018. Organized by the WHO regional offices for South-East Asia and the Western Pacific, it brought together participants from the six GMS countries: Cambodia, China, Lao People’s Democratic Republic, Myanmar, Thailand and Viet Nam. The TES Network Meeting supports countries in monitoring progress and reviewing TES results as well as in planning and implementing future TES and integrated drug efficacy surveillance (iDES) activities over the next two years.

The emergence of multidrug-resistant malaria parasites in the GMS necessitates strengthening monitoring efforts. The drug resistance of antimalarial medicines is monitored by conducting TES. These aim to inform policy-makers about the efficacy of currently used drugs for evidence-based national treatment policy change, and to identify alternative artemisinin-based combination therapies (ACTs) for revision of national treatment guidelines, as necessary.

Surveillance for antimalarial drug efficacy through TES in burden reduction areas or iDES in pre-elimination areas is important to identify early deterioration of antimalarial drugs and update national treatment regimens promptly. Data from molecular markers, such as Kelch 13 (K13), also help to monitor drug resistance in the GMS.

During the TES Network Meeting, participants reviewed and discussed results from TES and iDES as well as molecular data for K13 and other markers. On the final day, country participants developed plans and budgets for TES and iDES implementation and monitoring for the next biennium.

The objectives of the meeting were:

- to review and discuss implementation and results of the recent TES and iDES in the GMS countries and discuss related implementation of other control activities;
- to discuss the role and results of K13, the molecular marker for tracking artemisinin resistance, and of other molecular markers for monitoring malaria drug resistance; and
- to develop GMS and country work plans and budgets for TES and iDES implementation and monitoring for 2019–2020.

Conclusions

Overview of GMS malaria elimination: GMS countries have achieved substantial progress towards malaria elimination, but significant transmission remains in some parts of Cambodia, the Lao People’s Democratic Republic, Myanmar and Viet Nam. The remaining challenges include: 1) sustainable financing; 2) project implementation in the remaining endemic areas and partnership coordination, 3) monitoring and addressing multidrug resistance, and 4) strengthening surveillance.

Status of artemisinin resistance: Artemisinin partial resistance alone does not affect the overall efficacy of ACTs if the partner drug remains effective. ACTs fail when parasites are resistant to the partner drug or to both artemisinin and the partner drug. In such cases, countries need to consider changing the first-line ACT.

TES results: Study results indicate that artemisinin partial resistance (presence of validated K13 mutants) and resistance to multiple partner drugs primarily affect the eastern part of the GMS (east of a vertical line drawn across Bangkok). In Cambodia, its adjacent provinces in the Lao People’s
Democratic Republic, Viet Nam and Thailand showed high failure rates for dihydroartemisinin-piperaquine (DHA-PPQ), which is the first-line drug in Viet Nam and Thailand. In the Lao People’s Democratic Republic, the efficacy of artemether-lumefantrine (AL) as a first-line drug is also declining. In Cambodia, artemether–mefloquine (ASMQ) and artesunate-pyronaridine (ASPY) are efficacious, while the other countries are currently monitoring their efficacy. Based on the absence of the *Plasmodium falciparum* multidrug resistance 1 gene (pfmdr1) copy number prevalence, ASMQ should be efficacious in all countries listed. Myanmar data showed high efficacy rates (more than 90% for AL, DHA-PPQ, ASMQ and ASPY).

**Quality control monitoring:** Quality control monitoring is important to ensure the quality of TES and iDES implementation, with a focus on the clinical and laboratory (microscopy and polymerase chain reaction (PCR) assays) outcomes, data validation, field coordination to facilitate patient enrolment, and regular on-site supervision to address field challenges. This monitoring allows for reliable data that can drive drug policy review/changes in a country.

**National treatment guidelines:** The GMS countries have different ACTs as first-line treatments. Most countries have quinine for seven days as a second-line treatment. However, the seven-day treatment with quinine is difficult to implement. All countries have low-dose primaquine (PQ) as a supplementary treatment for *P. falciparum*, but it is not yet operationalized in some countries. Training at health centres and in the community on the use and safety of low-dose PQ is crucial. All countries have PQ (14 days or 8 weeks) for radical cure of *P. vivax* in their national treatment guidelines. However, the implementation of this policy has been slow. In addition to the selection of drugs, other issues are critical to accelerate the elimination of malaria, such as universal access to prevention and treatment, functional community treatment networks, drug management (adequate stocks of ACTs and rapid diagnostic tests or RDTs in health centres and village malaria worker networks), and quality assurance of ACTs. Although the use of triple combination therapy (e.g. DHA-PPQ plus mefloquine) has been evaluated in some countries, the additional benefit (over ASMQ) is unclear if DHA-PPQ is no longer effective.

**Genetic markers:** Results from molecular marker analyses in Cambodia, the Lao People’s Democratic Republic, Myanmar and Viet Nam are largely in line with TES findings. Cambodia and Viet Nam showed high resistance rates against artemisinin and piperaquine, although Cambodia officially decided to stop the use of DHA-PPQ around three years ago. There are no or very limited signs of resistance against mefloquine and PYR. Results from the Lao People’s Democratic Republic did not demonstrate signs of resistance for the samples investigated. Of note, there were no K13 mutants detected in samples collected during the 2017 outbreak in Savannakhet. Results from Myanmar showed some resistance to artemisinin, but not to partner drugs.

**Transition to iDES:** As countries approach elimination and malaria transmission declines, strengthened surveillance systems can be used to collect and analyse data on drug efficacy. Through iDES, countries can transition from using a sentinel surveillance system to relying on efficacy data collected via the routine surveillance system. Thailand started piloting the feasibility of iDES in eight provinces in 2017; China is planning a pilot for iDES for imported *P. falciparum* and *P. vivax* cases.

**Recommendations**

Member States are encouraged to consider the following:

1) Continue monitoring the quality of TES implementation based on the WHO quality control checklist.
2) Continue efforts to strengthen microscopy quality assurance for TES and elimination purposes.

3) Review the results of TES within countries; consider switching the first-line drug, if the first-line drug is no longer effective nationally or sub-nationally.

4) Identify alternative ACT as second-line treatment, based on the TES results, and discontinue the use of quinine.

5) Accelerate the roll-out of glucose-6-phosphate dehydrogenase (G6PD) point-of-care (POC) tests (or other measures such as close monitoring) to enable the radical cure of *P. vivax* with primaquine.

6) Accelerate the registration process of all ACTs and test alternative ACTs in the TES.

7) Review and consider implementation of relevant recommendations from 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 (Phnom Penh, Cambodia, 26–28 February 2018).

WHO is requested to consider the following:

1) Share the latest TES template with all GMS countries.

2) Continue providing support for countries moving into elimination settings, particularly as they transition to iDES, including the finalization of the iDES protocol.

3) Review and revise national treatment guidelines based on available TES data and other information.

4) Support the full operationalization of revised national treatment guidelines with national programmes and partners, including low single dose of primaquine for *P. falciparum* infections.
1. INTRODUCTION

1.1 Background

Continued monitoring through therapeutic efficacy studies (TES) is a top priority for protecting the efficacy of antimalarial medicines. As the countries of the Greater Mekong Subregion (GMS) progress towards elimination, TES results are used to detect early declines in drug efficacy and to guide national treatment policies. During the Sixth Meeting of the GMS TES Network, participants met in Luang Prabang to review recent TES data and develop country-specific efficacy monitoring work plans and budgets for 2019.

Multidrug resistance, including resistance to artemisinin-based combination therapies (ACTs), has emerged in multiple areas of the GMS in the last decade. The recent Ministerial Call for Action to Eliminate Malaria in the GMS before 2030, signed by GMS ministers of health in May 2018, acknowledged that multidrug resistance is a serious concern for international health security. The Call for Action urged the immediate implementation of the WHO Strategy for Malaria Elimination in the Greater Mekong Subregion (2015–2030).

As countries approach elimination, lower malaria transmission will necessitate a shift away from TES towards integrated drug efficacy surveillance (iDES). Through iDES, routine monitoring of drug efficacy becomes part of the surveillance system in elimination settings. Molecular analysis provides an additional tool for tracking multidrug resistance. Data on genetic markers for resistance (such as Kelch 13) further enhance the monitoring of multidrug resistance.

1.2 Objectives

The objectives of the meeting were:

- to review and discuss implementation and results of the recent TES and iDES in the GMS countries and discuss related implementation of other control activities;
- to discuss the role and results of Kelch 13 (K13), the molecular marker for tracking artemisinin resistance, and of other molecular markers for monitoring malaria drug resistance; and
- to develop GMS and country work plans and budgets for TES and iDES implementation and monitoring for 2019–2020.

2. PROCEEDINGS

2.1 Opening session

Dr Juliet Anne Fleischl, WHO Representative, Lao People’s Democratic Republic, delivered the opening address on behalf of Dr Poonam Khetrapal Singh, WHO Regional Director for South-East Asia, and Dr Shin Young-soo, WHO Regional Director for the Western Pacific. She noted that GMS countries have made substantial progress in the last five years. As the Subregion moves closer to elimination, challenges still remain. National treatment guidelines (NTG) have yet to be fully operationalized in many GMS countries, and gaps in regulatory systems have led to the inappropriate use of medicines and the continued availability of substandard artemisinin-based combination therapies (ACTs) and oral artemisinin monotherapies. Not all ACTs recommended in national treatment guidelines have been registered in some countries, preventing the immediate utilization of
alternative ACTs if first-line drugs are no longer found to be efficacious. She encouraged GMS countries to jointly prepare for the next steps, as they review the results of TES and lay the foundation for appropriate national malaria treatment guidelines.

Dr Somphone Soulaphy, Chief, Division for Diseases Control, Ministry of Health, Lao People’s Democratic Republic, welcomed participants to the meeting on behalf of the Ministry. She thanked WHO for facilitating the two-day meeting. She emphasized that a key challenge in the GMS is countering drug resistance. It is critical for GMS countries to share experiences. Overcoming obstacles will require deep collaboration across borders. She stated that the Lao People’s Democratic Republic is proud to support the TES network meeting.

Dr Rabindra Abeyasinghe, Coordinator, Malaria, other Vectorborne and Parasitic Diseases, WHO Regional Office for the Western Pacific, outlined the three key objectives for the meeting. He noted that the GMS needs to work intensively to identify and address challenges. There are critical discussions that need to take place on how to operationalize findings and decide which changes to make to NTGs.

Dr Bouasy Hongvanthong, Director, National Malaria Control Program, Centre for Malariology, Parasitology and Entomology (CMPE), Lao People’s Democratic Republic, was nominated as Chair; Dr Preecha Prempree, Director, Bureau of Vector-borne Diseases (BVBD), Department of Disease Control, Ministry of Public Health, Thailand, was nominated as Vice-Chair; and Dr Huch Chea, Vice Director, National Centre for Parasitology, Entomology and Malaria Control (CNM), Cambodia, was nominated as Rapporteur.

The agenda and the list of participants are presented in Annex 1 and Annex 2, respectively.

2.2 Review of recommendations from 2017 and progress

Dr Dorina Bustos reviewed the recommendations for countries and for WHO from the fifth meeting of the GMS TES network in 2017. Countries were encouraged to continue efforts in strengthening implementation of high-quality TES using the standard WHO protocol; to strengthen laboratory capacities, particularly microscopy quality assurance (QA); and to implement quality control for molecular assays in collaboration with the regional reference laboratory at Institut Pasteur du Cambodge (IPC). Alternative ACT regimens need to be tested before declining efficacy becomes apparent. Countries were also encouraged to closely monitor TES implementation in the sentinel sites using the WHO monitoring checklist. A strong surveillance system needs to be in place to facilitate integration of drug efficacy monitoring into routine surveillance.

In 2018, quality TES are ongoing in four GMS countries: Cambodia, the Lao People’s Democratic Republic, Myanmar and Viet Nam. In these four countries, TES for artesunate + pyronaridine (ASPY) is ongoing, as well as for artesunate + mefloquine (ASMQ) in southern Lao People’s Democratic Republic. TES principal investigators and WHO are performing periodic quality control (QC) monitoring visits and supervision. In Thailand, iDES has been piloted in eight provinces (with Malaria Online). The Lao People’s Democratic Republic and Viet Nam are in preparation for using iDES in one to two provinces (using the District Health Information System, or DHIS2, platform).

An external competence assessment (ECA) has been undertaken for all six GMS countries (2017-2018) as well as a biregional international ECA (attended by Cambodia, Thailand, and Viet Nam). IPC has also assisted in implementing QC for molecular assays.
Following the recommendations for WHO in the previous TES network meeting, WHO has continued to provide technical assistance for TES (e.g. Cambodia, Myanmar, Lao People’s Democratic Republic and Viet Nam) and iDES implementation (e.g. Thailand and Yunnan Province). For the eight pilot provinces in Thailand, technical assistance included site visits, standard operating procedures (SOPs) and data analysis.

2.3 Update on antimalarial drug resistance including partial resistance to artemisinin and partner drugs in the GMS

Dr Pascal Ringwald presented an overview of treatment guidelines and definitions, noting the difference between full resistance and partial resistance. He also provided a summary of the molecular markers of artemisinin and partner drug resistance. In Cambodia, the percentage of parasites with the K13 molecular marker C580Y is over 90% in many areas. There continues to be a difference in genetic markers between areas to the east and to the west of Bangkok, whereby the east has a very high prevalence of a single K13 marker.

Dr Ringwald also presented data from areas outside the GMS, including data on K13 mutations in India and on ACT treatment failure rates in Africa. Additional data from Africa are needed to assess the relationship between dihydroartemisinin + piperaquine (DHA-PPQ) treatment failures and molecular markers. He called attention to the foci of artemisinin resistance that emerged independently in Papua New Guinea – demonstrating the risk of spontaneous emergence.

He summarized the clinical outcomes after ACT treatment according to the sensitivity pattern of each component, emphasizing that high treatment failures rates occur when there is both partial artemisinin resistance and partner drug resistance. He concluded with four key points: 1) data reaffirm the need for urgent and continued intensive regional malaria elimination in the GMS; 2) surveillance for artemisinin and partner drug resistance needs to be strengthened; 3) there is a critical need for surveillance outside the GMS for detecting potential de novo resistance or potential introduction of resistant parasites; and 4) where surveillance signals a potential threat to leading ACTs, effective alternative ACTs should be identified and implemented before resistance reaches critical levels.

Dr Abeyasinghe commented that in addition to drug monitoring, the issues of monotherapies and substandard drugs need to be addressed.

2.4 Strengthening coordination and partnerships to accelerate elimination in the GMS

Dr Hiromasa Okayasu presented on the three key areas of work of the WHO Mekong Malaria Elimination (MME) Programme: partnership coordination, advocacy and communications, and cross-country projects. Core activities include the annual Partnership Forum and the Regional Data Sharing Platform (RDSP). All GMS countries are now reporting monthly surveillance data to the RDSP. The programme also produces a quarterly MME Epidemiology Summary and biannual MME Bulletin. Dr Okayasu highlighted some of the remaining challenges in the GMS: ensuring sustainable funding; project implementation; monitoring and addressing multidrug resistance; and improving surveillance.

2.5 Monitoring drug efficacy: from TES to iDES into routine surveillance systems in areas close to elimination

Dr Ringwald discussed the differences between TES and iDES. TES is the gold standard for monitoring drug efficacy to inform treatment policy. The studies are conducted in sentinel sites and TES protocol can be adapted to different settings, with the main purpose of ensuring that a minimum
sample size is achieved for the sentinel site. Dr Ringwald stressed the importance of strengthening microscopy. He shared the TES template, encouraging GMS countries to use the latest template. He also highlighted the essential steps needed for ethical clearance and registration.

In areas nearing elimination, the surveillance system is strengthened to: improve case detection; increase reporting from all sectors; ensure that patients receive the full recommended treatment (including a radical cure); and confirm complete cure by follow-up at regular interviews. For these areas, the strengthened surveillance system can be used to also collect and analyse data on drug efficacy. Through iDES, all positive cases can be followed up to determine drug response. Efficacy monitoring is shifted from using a sentinel surveillance system to relying on data collected via routine surveillance systems.

Dr Ringwald stressed that iDES is not a simplified TES; rather, iDES is a surveillance activity. Integrating drug efficacy monitoring into the surveillance system involves ensuring that data collected on all malaria cases in the routine surveillance system can and are being used to also generate information about drug efficacy.

When shifting from TES to iDES, countries should ensure that they have a strong and functioning surveillance system. The system should be capable of reporting on all cases of malaria, providing all cases with supervised treatment, following up on patients and data collection and analysis by the national malaria control programme. The shift to relying on data from routine systems for iDES typically only occurs when there are too few cases to have a functioning sentinel site surveillance system, and when available resources allow for monitoring of the remaining few cases.

While the procedures for collecting drug efficacy data may vary between countries (depending on systems in place and resource availability), there are mandatory activities, including: patient classification; diagnosis on day 0 by rapid diagnostic test (RDT) and/or microscopy; microscopy diagnosis on final day of follow-up; glucose-6-phosphate dehydrogenase (G6PD) test for Plasmodium vivax (Pv) patients; supervised treatment including primaquine (PQ) for Pv patients; supervised second-line treatment and follow-up in case of treatment failures; end-date follow-up period at day 28 or day 42 (depending on half-life of drugs given) for Plasmodium falciparum (Pf) cases and at day 28 and 6 months (for relapse) for Pf cases; and end-date defined as final day of the follow-up period with cure, or any day the patient presents with recurrent parasitaemia after a treatment (additional full follow-up period is needed with new treatment). During the follow-up days, information on clinical symptoms temperature and parasitaemia at day 0, end-day or any day of recurrent parasitaemia should be recorded.

In addition to the mandatory activities, there are other recommended activities such as additional follow-up for Pf cases on day 3 and then weekly on days 7, 14, 21, 28, 35 and 42 (49, 56) and follow-up for Pv on days 7, 14, 21 and 28 and monthly. Blood collected at day 0 and day of failure can also be used for analysis of markers of reinfection/recrudescence, of drug resistance and of the geographic origin of the parasite.

Continued analysis of data is essential for detecting the presence of treatment failures and programmatic issues (e.g. percentage lost to follow-up and whether second-line treatment was given as per the national treatment policy). In addition to continued analysis, it is necessary to define the time point whereby data are reviewed and discussed.

Dr Hongvanthong emphasized the importance of applying lessons learnt from Thailand’s iDES. He stated that countries need support from WHO and partners as well as information-sharing from other
GMS countries. Dr Sintasath (United States Agency for International Development/President’s Malaria Initiative) added that iDES can serve as the backbone of surveillance in the GMS.

Dr Ringwald clarified that the current certification requirements do not require iDES and that countries may adapt different variants of iDES as numbers decrease. However, certification will require that the country can demonstrate that every case was followed up and cured.

Dr Sintasath also asked about iDES in the context of forest-goers. Dr Abeyasinghe noted that there are several types of forest-goers who engage in different activities. They also spend different amounts of time in the forest areas. A stronger evidence base is needed to better understand malaria transmission in forest-goers.

Ms Dantzer from the University of California, San Francisco (UCSF) shared information on the research undertaken for a community randomized controlled trial by UCSF and CMPE in Champasak Province, Lao People’s Democratic Republic. The research aims to evaluate the effectiveness, cost-effectiveness, acceptability and feasibility of two targeted test-and-treat interventions using highly sensitive RDTs (HS-RDTs). One intervention is focal test-and-treat led by peer navigators who travel into the forest and other non-village areas and survey, test and treat high-risk population members. The second intervention is village-based mass test-and-treat (MTAT), which surveys and tests all households in half of the 56 study villages.

2.6 Presentations by principal investigators in the GMS on TES results

Cambodia – Dr Rithea Leang

Dr Leang presented a brief overview of drug resistance in Cambodia, noting that between 2000 and 2016 the country had changed three ACTs. In 2016–2017, Cambodia reintroduced ASMQ (first procurement in eight provinces in February 2016 and second procurement for entire country in August 2017). Other ACTs were tested as future options in 2016, and artesunate + amodiaquine (ASAQ) showed failure rates of 14% (D42) and 23% (D42) in Pursat and Mondulkiri, respectively. TES results from 2016 demonstrated full efficacy for ASMQ in two sites and also confirmed high DHA-PPQ failure in the north-east. ASMQ continued to demonstrate 100% efficacy in the 2017 TES. Dr Leang also shared the data on ASPY from two sites: Rattanakiri (adequate clinical and parasitological response (ACPR) of 98.3% at D28 and 96.7% at D42) and Mondulkiri (ACPR of 100% at D28 and 98.3% at D42).

This year, ASMQ is being investigated in three sites (Rattanakiri, Mondulkiri and Kratie) and ASPY in two sites (Kampong Speu and Pursat). Data demonstrate the increasing proportion of Pv cases in Cambodia. Dr Leang presented three major conclusions: 1) ASMQ is highly effective in the western, northern and southern parts of Cambodia; 2) ASPY is the potential alternative ACT in the north and east of Cambodia; and 3) ASMQ needs to continue to be closely monitored and alternative ACT explored.

In response to a question, Dr Leang commented on the multiple factors that help to explain why cases are increasing. A major factor is the disruption of the village malaria workers programme. He also noted data do not suggest that drug resistance is correlated with the increased cases. Dr Ringwald highlighted that the number of Pv cases significantly increased, and Pv is not presently affected by drug resistance in Cambodia.
**Lao People’s Democratic Republic – Dr Vonethalom Thongpaseuth**

During the last five years, Pf cases have been reduced by approximately 80% in the Lao People’s Democratic Republic. The total number of malaria cases was 9336 (of which 4554 were Pf) in 2017.

Dr Thongpaseuth discussed TES results from 2016–2017 in two sentinel sites. In Champasak, TES results for DHA-PPQ demonstrated an ACPR of 56%. The samples demonstrated a high K13 mutation rate (83%) and Pfpm2 amplification (60%). Results from Salavan province demonstrate an ACPR of 83% for artemether-lumefantrine (AL) and K13 mutation rate of 50%. Estimates for the current TES in 2018 (ASPY in Salavan and ASMQ in Champasak) are not yet available.

Dr Thongpaseuth highlighted several major challenges: the low number of clinical cases in sentinel sites, maintaining high-level microscopy, coordination between health centre staff and district staff for case referral, and follow-up of recruited cases. To resolve these issues, there are critical next steps for the Lao People’s Democratic Republic, such as strengthening collaboration between public and private sectors for case referrals, expanding microscopy refresher training and strengthening the QA process.

Institut Pasteur du Laos and the Japan International Cooperation Agency (JICA) conducted research on five southern provinces (2015–2016) to monitor the prevalence of drug-resistant mutations. Preliminary results show that 72.5% of samples from Champasak have K13 mutations (mainly C580Y). Other research by Lao-Oxford-Mahosot Hospital Wellcome Trust Research Unit (LOMWRU) has been used to generate a “genetic report card” for the southern provinces in the country. Data from Champasak demonstrate high resistance (artemisinin clearance = 83%; PPQ resistance = 81%; DHA-PPQ failure = 79%; and sulfadoxine resistance = 95%).

Dr Thongpaseuth stated that DHA-PPQ will not be considered as an option for first-line treatment. She also summarized the decreasing therapeutic efficacy of AL as a first-line drug for treatment of Pf malaria.

Dr Hongvanthong commented on the importance of coordinating with partners, such as JICA, for better data-sharing. He also asked Dr Ringwald for his opinion on explanations for the high failure rate of DHA-PPQ in the Lao People’s Democratic Republic. Dr Ringwald highlighted that there could be multiple explanations. One explanation could be the availability of unregulated DHA-PPQ. Thus, DHA-PPQ may have been circulating in some areas for several years despite the drug not being registered. This would require investigation.

Another explanation is that patients may have acquired malaria in Cambodia or in the forested areas along the border. Dr Bustos commented that most failures were in districts where many people (e.g. loggers) have travelled across the border to Cambodia. Dr Witkowski noted that the data are consistent with the treatment failure rate across the border in Cambodia.

Dr Iwagami added that comparisons of genetic information from parasites also appear to support the explanation that people may be infected in Cambodia. Based on comparisons of artemisinin-resistant parasites from Cambodia and from the Lao People’s Democratic Republic, most Lao parasites are genetically identical, or very similar, to those from Cambodia.

**Myanmar – Dr Aung Thi**

Although Myanmar has substantially reduced the number of malaria cases, 291 townships (of 330 total) remain malaria endemic. Last year, 85 019 malaria cases were reported, the majority (60%) of which were Pf.
Results from TES (2017–2018) demonstrate that first-line antimalarial treatments for Pf are efficacious. ASPY showed 100% efficacy in Naung Cho (Kachin state), Moe Nyin (northern Shan state), Kawthoung (Tanintharyi region) and Myawaddy. Dr Thi noted that ASPY is also showing 100% efficacy in two study sites that are ongoing. TES results for AL demonstrated an ACPR of 93.02% and 93.3% for Naung Cho and Moe Nyin, respectively.

The 2017–2018 TES results for chloroquine (CQ) treatment for Pv demonstrate that CQ sensitivity decreased in the Tanintharyi region (ACPR 93.2%). There was unusual seasonal increase of Pv in two townships during 2018. In the Kayin state study site, CQ demonstrated 100% efficacy.

The prevalence of K13 mutations showed the emergence of mutations in different areas, except in the western border. The F446I mutation was reported in 8.3% of samples from Beelin and 44.7% of samples from Myawaddy. In samples from Kawthoung, 26.9% of samples had the C580Y mutation. K13 mutations have not been associated with clinical failures.

Dr Thi raised a number of challenges with TES, such as inadequate number of cases, access to hard-to-reach areas, shortage of technical staff and funding transfer delays. He also highlighted results from a cross-sectional study (2017–2018) on sustainable access to PQ in Myanmar. Some of the issues identified by the study were the loss of follow-ups (especially in conflict areas) and delays in timely substitution of new stocks for PQ.

Dr Ringwald commented that the Myanmar data further demonstrate the different situation of drug resistance to the west of Bangkok. Whereas in Cambodia, the percentage of C580Y is at least 80% in some areas, the highest percentage reported for Myanmar was only 26.9%.

**Viet Nam – Dr Huynh Hong Quang**

Over the past 10 years, the number of malaria cases has decreased by 72.2% in Viet Nam. Between 2012 and 2017, the main objectives of the country’s TES activities have been to assess the efficacy of DHA-PPQ for the treatment of uncomplicated Pf malaria and to assess the efficacy of CQ for the treatment of Pv. In 2016, the provinces of Binh Phuoc and Dak Nong demonstrated low efficacy rates for DHA-PPQ of 53.7% and 73.3%, respectively.

TES results from last year demonstrate an ACPR of 81.8% for DHA-PPQ in Binh Phuoc and of 90.9% in Dak Nong. Khanh Hoa, Gia Lai and Ninh Thuan reported 100% efficacy for DHA-PPQ. In 2017–2018, ASPY TES were undertaken in five provinces. Preliminary results from Khanh Hoa and Ninh Thuan demonstrated 100% efficacy and Binh Phuoc, Gia Lai and Dak Nong reported an ACPR of 93.5%, 98.4% and 83.3%, respectively. Dr Quang also shared genetic marker data from Binh Phuoc (2016–2017). Of the samples tested, 91% had K13 mutation (90.5% C580Y) and 54.3% demonstrated PPQ resistance (PfPm2 amplification).

Challenges for TES implementation are reduced Pf and Pv cases and obtaining minimum sample sizes. Dr Quang summarized the achievements as close collaboration with the government and private sector for patient recruitment and short course (seven days) TES for rapid evaluation. He said that potential suggestions for improvement include modified in vivo test in the short course and tracking molecular markers.

There are multiple studies for operational research, such as the G6PD deficiency survey completed by the National Institute of Mariology, Parasitology and Entomology (NIMPE) and genetic markers study by Institute for Malariology, Parasitology and Entomology (IMPE), Oxford University Clinical Research Unit (OUCRU) and others. Clinical trials with triple combination ACTs are ongoing by OUCRU. The trials include DHA-PPQ plus mefloquine (MQ) (three days), which is completed and
awaiting publication. The other ongoing trial in Binh Phuoc is for the triple combination of AL plus amodiaquine (3 days).

Dr Ringwald asked for clarity on the meaning of the seven-day TES. The speaker said it is a modified protocol that allows the evaluation of parasite clearance time, D3 positivity and K13 mutations. Dr Ringwald commented that parasite clearance and molecular markers are not alone sufficient for predicting drug efficiency; efficacy also takes into account many other factors. He stressed that an in vivo test cannot be replaced with molecular markers. Furthermore, not all drugs have identified markers (e.g. AL). Dr Ringwald also emphasized that it is necessary to evaluate the partner drug over a longer period of follow-up, not a seven-day TES.

Dr Ringwald asked whether there is a comparative arm for the testing of DHA-PPQ plus MQ. The speaker clarified that there is a comparative arm with DHA-PPQ. Dr Ringwald asked whether there were plans to adopt the triple combination. He also requested feedback from countries on the role of triple combination therapies.

Dr Ringwald cautioned that using DHA-PPQ in the triple therapy places very high pressure on DHA-PPQ in an area where there is already resistance. He noted that it is most likely the MQ component of the therapy, not the triple therapy itself, which is efficacious. MQ is virtually acting as a monotherapy, and, as such, the absence of MQ resistance may drive the efficacy of DHA-PPQ + MQ.

Dr Abeyasinghe added that one purpose of the triple therapy is to combine drugs for a synergistic effect. Because DHA-PPQ is already failing, the triple therapy is not achieving a synergistic effect; it is achieving the effect of a monotherapy.

Dr Okayasu asked about the continued use of DHA-PPQ despite the lower efficacy. Dr Quang explained that since 2016, the country has changed the policy for DHA-PPQ. Nevertheless, there are issues with registration and procurement of alternative ACTs. The quantity of drugs required by Viet Nam is very small compared to the quantity of drugs required by manufacturers as a minimum order size (e.g. 1 million doses).

Dr Abeyasinghe cautioned that there is the potential to repeat previous mistakes in Cambodia, where DHA-PPQ had also been failing. A representative from the Global Fund to Fight AIDS, Tuberculosis and Malaria emphasized that this is a crucial issue to resolve.

### 2.7 iDES and QC in TES implementation

**Yunnan, China – Dr Fang Huang**

China reported no indigenous cases for 2017. Between 2010 and 2017, the number of reported cases declined substantially from 64 178 to 2675 cases. Of the 2675 reported cases in 2017, 2672 were imported and three were caused by infection via blood transfusion.

Although the number of locally acquired cases has reached zero, imported cases continue to be a major challenge. The majority of cases (84.5%) are imported from Africa, and 13.6% are imported from South East Asia (with Myanmar alone accounting for 10.2%). Thirty-one provinces reported imported cases, and the top seven provinces account for 61% of all cases. Dr Huang highlighted the examples of Shanglin County where 65% of cases were imported from Ghana and Yingjiang County where 77% were imported from Myanmar.

Under China’s current NTG, Pf is treated with ACTs (DHA-PPQ, AS-AM and AS-PIP) or pyronaridine + PQ. Treatments for Pv, *P. ovale* and *P. malariae* include CQ + PQ (eight days), or
PPQ/pyronaridine/ACTs for CQ treatment failure. TES results (2016–2017) demonstrate 100% efficacy for DHA-PPQ in Yingjiang, Yunnan Province.

Dr Huang highlighted the progress, issues and bottlenecks with piloting iDES. There is a need for technical support and training. Two key issues are funding and difficulties with patient follow-up (e.g. when a patient moves along the Myanmar border). She said that they aim to start iDES next year.

She described the protocol for the pilot iDES in China. On D0, two thick and thin blood slides and three dried blood spots (DBS) on filter paper will be obtained from patients with uncomplicated Pf malaria. Patients will receive supervised treatment by staff and a follow-up schedule will be established for days 3, 7, 14, 28 and 42. During the subsequent follow-up days, the same number of blood slides and DBS will be obtained, along with the drug efficacy surveillance form.

Thailand – Dr Aungkana Saejeng

Thailand commenced iDES in three pilot provinces (Chiang Mai, Chiang Rai and Mae Hong Son) in May 2017. Later that year, iDES was scaled up to another five provinces. Dr Saejeng presented the iDES workflow in hospitals and in malaria clinics. She emphasized that routine follow-up is a key element of case management within the NTG.

During each follow-up day, two blood slides (thick and thin) and three blood spots on filter paper are collected. There is also a follow-up form and a drug bag with information on completing the medication, the scheduled days of follow-up and the results of G6PD testing. The iDES reporting form collects information such as history of treatment, body temperature, parasitaemia, side-effects and the health-worker checklist for sample collection.

She presented data over the course of the two-year period for iDES (from October 2016 to August 2018). She outlined the methodology, including: treatment information from NTGs, follow-up schedule (Pf was D0, D3, D7, D28, D42 and Pv was D0, D14, D28, D60 and D90); and survival analysis for treatment efficacy (Pf endpoint day 42 and Pv endpoint D60). Although DBS was collected for polymerase chain reaction (PCR), this has not yet been completed.

Of the 2868 patients, there were 484 Pf cases, 2354 Pv cases, and 30 other and mixed infection cases. The province of Sisaket, which borders Cambodia, reported the highest number (43%) of cases. The median age of patients was 33 years. The vast majority of patients were male (80%) and Thai nationals (82%). Of the total patients, 38% were diagnosed in hospitals.

ASMQ radical efficacy against Pf was 97.8%, with one recurrent Pf in Mae Hong Son. DHA-PPQ radical efficacy was 94.8% overall; however, Sisaket demonstrated a significantly lower efficacy for DHA-PPQ (78.6% by D42). Five recurrent Pf were reported in Sisaket only. CQ also demonstrated a significantly lower efficacy in Sisaket (37.8% at D90) for Pv. There was one recurrent Pv from Mae Hong Son, and 30 recurrent Pv from Sisaket.

Overall, the radical treatments (Pf and Pv) performed well except in Sisaket. It is recommended to review Pf and Pv treatments in this province. It is also recommended to measure the representativeness of the sample for robust evidence-based drug efficacy assessment between the follow-up sample and the overall malaria population (malaria indicator survey data source results, 2018) in terms of species, age, gender, nationality, and place of treatment and follow-up.

Dr Ringwald thanked Thailand for demonstrating the feasibility of iDES. He agreed with the need for additional data from Sisaket. Dr Saejeng clarified that it is only in Sisaket that they have found treatment failures with DHA-PPQ. Dr Ringwald suggested that Thailand request the Armed Forces
Research Institute of Medical Sciences (AFRIMS) to assist with an analysis of molecular data from the Sisaket sample. Such analyses could examine molecular markers of resistance and investigate whether the five cases were the result of reinfection or recrudescence. He emphasized that it is critical to have second-line drugs available so that patients, as in those five patients in Sisaket, can be treated immediately and later followed-up again.

Dr Ringwald encouraged other GMS countries to start pilot studies on iDES and to draw on the lessons from Thailand’s work on iDES over the last two years.

QC in TES and iDES: implementation challenges

Dr Bustos reviewed the WHO in vivo protocol for the assessment of therapeutic efficacy. Designed for Pf and Pv as well as all drugs (including CQ), the protocol is the standard guide to monitoring the efficacy of antimalarial drugs in order to update drug policy. The protocol has been adopted by national malaria control programmes and research institutions and has been updated by the WHO Ethics Review Committee. WHO provides additional tools for in vitro tests and parasite genotyping.

For countries reaching elimination levels, iDES involves routine monitoring of the efficacy of first- and second-line drugs as part of the surveillance system. Key facets of a strengthened surveillance system include: monitoring of all malaria cases; supervised treatment; follow-up at 28 or 42 days (end point); and molecular markers as additional tools. Three prerequisites for iDES have been identified: a case-based surveillance system with patient unique identifier (ID number); quality-assured microscopy skills at district level; and follow-up for all patients.

WHO developed QC monitoring checklists for pre-study, during the study (interim) and at the end of the study. An additional QC report by external clinical monitors was developed and used in Bangladesh, Cambodia, the Lao People’s Democratic Republic, Myanmar, Thailand and Viet Nam. There are four major components of the QC interim study checklist: general study information; study sites and site-specific information (e.g. site staff training; facilities; resources; and drug inventory); study-specific information (e.g. ethics documents and protocol, patient recruitment and follow-up, protocol compliance and case report forms, laboratory and microscopy, and data entry); and conclusions/comments/action items.

QC monitoring has identified some common issues with case report forms, informed consent/assent forms, laboratory procedures, drug treatment and thermometers/temperature recordings. For drug treatment, there have been instances where second-line drugs were not available in district hospitals. It is important to call attention to this problem of availability not only with the team leader but also with the programme. There are also instances where PQ treatment has not been recorded. Untrained staff as well as thermometers that have not been properly calibrated pose problems for accurate temperature readings.

During the preparation phase of TES, common challenges include protocol development and review/approval by national committees and the WHO Ethics Review Committee, as well as administrative delays in release of funds and clinical trial registration. With regard to protocol development, Dr Bustos encouraged countries to refer to the latest TES template 2018 v1.5.4, accessible on the WHO website.

A critical issue with TES implementation is the need for regular supervisory visits by principal investigators and medical monitors. Other issues during implementation include: adherence to the study protocol (e.g. documentation and reporting system); securing consent for pregnancy tests; and patient follow-up (especially in remote areas).
There are also laboratory challenges related to: microscopic blood examination (e.g. poor slide preparation and missed mixed infections); filter papers for DBS samples (e.g. inadequate size of filter paper and improper labelling and storage); QA/QC of molecular procedures; and material transfer agreements (MTAs) between country and reference laboratories.

Dr Bustos commented on the importance of follow-up procedures for febrile and afebrile patients in the GMS. Due to high D3 positivity in the GMS, smears and temperature checks should be repeated until negative for non-febrile cases, with follow-up weekly to D28/42.

Dr Bustos described additional challenges for non-TES-related activities. Some researchers are validating microscopy by PCR, which leads to difficult interpretation. Comparative trials for surveillance are not recommended. Adding further research questions to TES not only increases the burden on staff but also compromises the quality of TES implementation.

Dr Abeyasinghe commented that it is crucial for principal investigators to visit all sites and that it is not clear how many site visits they are making.

### 2.8 Summary of results from GMS countries

Dr Ringwald presented a summary of the treatment policies for Pf malaria and of the TES results by country (see Annex 3).

In Cambodia, ASMQ is the first-line treatment for Pf while quinine + tetracycline (QN+T) and quinine + doxycycline (QN-DX) are second-line. ASAQ and ASPY (in the east) have been found to be efficacious. DHA-PPQ, ASAQ, AL (although borderline) and ASPY (in the west) have been found to be failing.

In the Lao People’s Democratic Republic, AL is first-line and QN-DX is second-line. Both AL and DHA-PPQ are failing in the country; however, the result for DHA-PPQ is limited by a small sample size. More evidence on the efficacy rates of AL is still needed from the rest of the country.

Myanmar has AL, ASMQ and DHA-PPQ as first-line, with quinine + doxycycline as second-line. All of the first-line drugs, along with ASPY and ASAQ, have been found to be efficacious.

In Thailand, DHA-PPQ is first-line, with second-line treatments including QN+CL/DX/T, AS+CL/DX/T, AP and AL. DHA-PPQ, ASMQ, ASPY and AL (borderline) have been found to be efficacious. At the same time, however, DHA-PPQ has been found to be failing in Sisaket. Past TES showed ASMQ is failing in some parts of the country, especially the western border with Myanmar, and the Trat–Pailin border with Cambodia.

In Viet Nam, DHA-PPQ is first-line and second-line treatments are ASMQ, ASPY, AL and ASAQ. ASPY, ASMQ, and ASAQ (although older data) have been found to be efficacious. While DHA-PPQ is efficacious in some provinces, it is failing in others (e.g. Binh Phuoc).

Dr Ringwald highlighted four key conclusions. First, NTGs are not fully operationalized (with quinine as a second-line) or there are delays in operationalization of the updates (e.g. DHA-PPQ used until 2017 in Cambodia). Second, the quantification of antimalarial medicines in most GMS countries is determined based on historical epidemiological data. Third, PQ regimes have been implemented for all forms of malaria. And fourth, coordination between the national malaria control programme, food and drug administration, and procurement is absent.

There are potential options for new policy treatment, including ACTs for first- and second-line treatment, triple combinations, and double ACTs sequentially. Dr Ringwald requested that countries
share their comments and feedback about these three options. Most countries have quinine as second-line, yet it is very difficult to implement (given the treatment regimen).

2.9 Updates from the malaria program managers’ meeting of malaria endemic countries of the Western Pacific Region in relation to drug policy implementation – Q&A

Dr Abeyasinghe presented a summary of NTGs for Cambodia, the Lao People’s Democratic Republic and Viet Nam as well as an overview of TES results for the three countries.

Cambodia previously faced a major time gap between the decision to implement a new first-line treatment and the implementation of the decision. Currently, the country faces another gap between the decision to use 14-day PQ treatment against Pv and the full operationalization of the treatment. Given the increase in Pv cases, implementing and ensuring compliance with PQ is a critical challenge to overcome.

He also commented on the findings from his site visits in Cambodia, where three of the four sites faced drug stock-outs. One issue is that drug quantification is based on historical data. There was also the misuse of the second-line treatment; some patients would receive incomplete treatment with quinine + doxycycline. The distribution of village malaria workers was a further challenge. Optimal use of the village malaria workers programme is important to ensure that the network actually expands access to malaria services and commodities to the most at-risk populations.

Dr Abeyasinghe additionally called attention to case management in the Lao People’s Democratic Republic. When comparing the number of cases tested by sector, the Government tested 84.3% in 2017, but the percentage of cases treated was 69.6%.

For Viet Nam, there is a worrying trend of the continued use of DHA-PPQ amidst its declining efficacy in TES. This trend is particularly concerning because of the lessons learnt from Cambodia. Dr Abeyasinghe also pointed out the substantial mismatch between the number of cases from 2015 to 2017 and the number of tablets used (1.173 million). The majority of case management is undertaken by community health workers: 66% of total tested and 63% of total treated in 2017.

Dr Abeyasinghe presented on the foundational guidelines for recommendations and therapeutic objectives. He emphasized four core principles: early diagnosis and prompt effective treatment (within 24–48 hours of onset of malaria symptoms); rational use of antimalarials (e.g. reduce the spread of drug resistance, limit wastage, effective case management of febrile illness and universal access to parasitological diagnosis); combination therapy (for improved efficacy and to prevent resistance); and appropriate weight-based dosing (to prolong the useful therapeutic life of medicines). The therapeutic objectives of uncomplicated Pf malaria and uncomplicated Pv malaria are to cure the infection as rapidly as possible, to reduce transmission and to prevent the emergence and spread of antimalarial drug resistance.

Ensuring antimalarial drug quality and universal diagnosis testing of all suspected malaria cases are critically important. National drug and regulatory authorities should be supported to ensure that the antimalarial medicines provided in private and public sectors are of acceptable quality through regulation, inspection and law enforcement. This includes preventing the availability and use of oral artemisinin monotherapies, ensuring counterfeit/falsified and substandard antimalarials are not in the market, as well as prequalification of ACT manufacturers. The regular conduct of TES using standard WHO protocols is vital to ensuring antimalarial drug quality.
Dr Ringwald encouraged countries to be more proactive and to learn from the experience of Cambodia. He stressed that WHO will support the GMS countries to update NTGs in order to ensure effective treatments.

Dr Rithea Leang explained that the low single dose PQ is in the guidelines for Cambodia but not operationalized. He emphasized that health centre staff need to be well-informed and properly trained; instructions are only paper based, and some staff are reluctant as they do not feel knowledgeable enough. With regard to triple therapy, he commented that more information is needed. He requested that WHO consider which components could be combined to replace quinine as second-line treatment.

Dr Hongvanthong spoke on the issue of not changing AL despite the TES results in the Lao People’s Democratic Republic. He emphasized that there are numerous factors, such as the lack of very strong evidence for the Ministry of Health. The country is testing ASPY and ASMQ in order to provide results to the Ministry. Another factor is the cost of training for central, provincial and district levels. He noted that updating the treatment guidelines could still take two years. A third issue is the lag between updating treatment guidelines, training the staff and procuring the drugs. There is already the problem of ASPY expiring in October this year (over 100,000 tablets).

Dr Hongvanthong also posed the question of which drugs should replace quinine as second-line treatment. Dr Ringwald noted that the Lao People’s Democratic Republic has multiple options and that these options could be discussed at a further meeting.

Dr Tran Cong Dai and Dr Huynh Hong Quang commented on the use of DHA-PPQ in Viet Nam. The country has discussed about drug replacement in drug-resistant areas. The plan is to optimize by the end of this year based on the current ASPY TES. Recruitment for testing of ASPY has been a challenge.

Dr Preecha Prempree noted that procurement takes six to eight months in Thailand. Because of this delay, there is less time for the drug to be used and there is a need to prepare very early with estimated drug quantities.

Dr Ringwald commented on the urgent need for data-sharing of the situation in Sisaket. It would be useful to consolidate available data (e.g. from national programmes and research institutes). It is important to have a clearer picture of where patients are coming from, as well as information on molecular markers for PPQ resistance. Dr Sintasath noted the opportunity for a meeting to discuss all relevant results in order to reach decisions on actions moving forward.

2.10 Updates on K13, plasmepsin and other molecular markers for resistance in the GMS

Dr Benoit Witkowski presented data from TES and surveys in the GMS from the investigation program of IPC (2017–2018). He summarized the three molecular markers for resistance in the GMS: K13 polymorphism for artemisinin derivatives, Pfpm2/3 amplification for PPQ, and Pfmdr1 amplification for mefloquine. There are no markers yet established for lumefantrine, amodiaquine and pyronaridine.

Results from Cambodia showed high therapeutic efficacy for ASPY (ACPR of 96.6%) and ASMQ (ACPR of 98.2%) in 2017. There is a high prevalence of artemisinin resistance (75.5% K13 mutants, with C580Y accounting for 71.7%). Dr Witkowski posed the question whether this constituted a plateau or it will change. Cambodia also demonstrates a high prevalence of PPQ resistance (69.3%) and very limited MQ resistance.
TES data from Viet Nam demonstrated very similar results to Cambodia: a high prevalence of artemisinin resistance (66% K13 mutants, with C580Y accounting for 59.2%) and PPQ resistance (51.1%), with very limited resistance to mefloquine.

In the Lao People’s Democratic Republic, a resistance markers survey was conducted on an outbreak sample from Savannakhet province. The investigated samples did not demonstrate resistance. However, Dr Iwagami noted that most artemisinin-resistant strains are in southern Lao People’s Democratic Republic.

Myanmar TES data demonstrated resistance to artemisinin (43.7% K13 mutants) but no resistance to partner drugs (for the markers considered). As with Cambodia and Viet Nam, the K13 markers were site specific. R561H accounted for 36.6% and F446I accounted for 7.0% of K13 mutants. Dr Witkowski noted that more evidence is needed on R561H.

Dr Witkowski summarized additional conclusions in terms of novel therapeutic options and resistance evolution. ASPY represents a relevant alternative for drug resistance areas (including ART resistance, PPQ resistance and MQ resistance). At the same time, surveillance remains necessary for the emergence of PYR resistance in case of widespread implementation. With regard to resistance evolution, the presence of double amplified strains is very limited with an unclear clinical impact. Highly AQ-resistant strains circulate in Cambodia.

Dr Ringwald commented on the added value of molecular markers in the investigation of outbreaks. The molecular data from the Lao People’s Democratic Republic suggest that drug resistance did not cause the Lao outbreak, because there is no evidence of drug resistance from the samples tested. The outbreak was most likely caused by other factors. Similarly, the molecular data in Cambodia suggest that, if the first-line treatment was followed with MQ (i.e. if DHA-PPQ was not used), then the outbreak in Cambodia was also not caused by drug resistance, because there is very limited resistance to MQ.

Dr Ringwald noted that molecular markers are an important asset, but emphasized that they are not predictive of treatment failures. The presence of a mutant strain is a negative predictor, not a positive predictor.

2.11 Presentation of country plans for TES (country principal investigators)

Cambodia

For 2019, Cambodia will conduct TES in six sites, testing ASPY in two sites (Stung Treng and Oddar Meanchey) and ASMQ in four (Modulkiri, Pursat, Kampong Speu and Takeo). In 2020, the country will test ASPY in two sites (Pursat and Kampong Speu) and ASMQ in four sites (Siem Reap, Kratie, Rattanakiri and Takeo). The implementers for TES will be the National Centre for Parasitology, Entomology and Malaria/Ministry of Health. Monitoring and supervision will occur on a monthly basis, and refresher microscopy training is planned for all sites. In Takeo, there is additional need for iDES training.

China (Yunnan)

In Yunnan Province in 2017, 326 cases were reported from 33 counties in 13 prefectures. Yingjiang accounted for the majority of cases (179 cases), with the remaining cases from Tengchong (28 cases) and Ruili (15 cases). Of the 326 cases, the vast majority (87%) were imported from Myanmar. The pilot iDES in Yunnan will involve additional protocol to China’s “1-3-7” surveillance strategy. Within the first day of 1-3-7, two thick and thin blood slides and one DBS will be obtained.
Supervised treatment on D0 will occur by staff, and a follow-up schedule will be set-up for days 3, 7, 14, 28 and 42. On the follow-up days, two thick and thin blood slides and one DBS will be taken, and data will be recorded on the drug efficacy surveillance form. All follow-up samples will be confirmed by the malaria reference lab, with the data entered into the iDES database.

**Lao People’s Democratic Republic**

The TES plan for the Lao People’s Democratic Republic in 2019 will involve three sites (Champasak for ASMQ and AL; Salavanh for ASPY and ASMQ; and Savannakhet for AL). In 2020, the county will conduct TES for three sites, with the same drugs tested in the Champasak and Savannakhet sites and with ASMQ tested in Sekong. The implementers will be CMPE for Champasak and Savannakhet and Institut Pasteur du Laos for Salavanh. The country will test iDES in 2019 in Luang Prabang for AL. Target enrolment will be for all cases.

Dr Ringwald commented that the sample size has been very limited for the Lao People’s Democratic Republic. He noted that limited sample sizes have the potential to lead to overestimations of treatment failure.

**Myanmar**

In 2018–2019, Myanmar will conduct TES in Tamu (Sagaing), testing AL and DHA-PPQ; Buthidaung (Rakhine state), testing APYR and CQ; and Kawthaung (Tanintharyi region), testing APYR. For 2020, Myanmar will conduct TES in Naung Cho (Northern Shan) for AL and CQ and in Buthidaung (Rakhine state) for AL.

**Thailand**

In Thailand, iDES will be called “case follow-up”. The country is working on improving the iDES standard operating procedures, including all levels from peripheral, regional and national. Several areas of improvement have been identified: reporting forms to be simplified and standardized; standard operating procedures to be reflected as part of the surveillance manual, with possibility for inclusion to the national treatment guidelines; for the second-line treatment to be included in the case follow-up; and for analysis to be based on case classification and recurrence or relapse. For DBS, the standard operating procedures will also clearly outline the role of regional and BVBD laboratories. Thailand will be scaling up iDES to cover the entire country and all cases of malaria (all species).

The country aims to improve timeliness through the 1-3-7 notification, especially from hospitals, to ensure patients are placed on follow-up schedules. For better case monitoring at service facility level, the malaria information system (MIS) dashboard and data analysis visualization will be improved. In parallel, the country will work on laboratory strengthening for microscopy QA and the national malaria reference laboratory (NRL).

**Viet Nam**

In 2019, Viet Nam will undertake TES in four sites, testing ASMQ in Binh Phuoc and Dak Nong; ASPY in Gia Lai; and DHA-PPQ in Dak Lak. The country will conduct iDES in two sites (Quang Tri and Phu Yen), testing DHA-PPQ. In the following year, the country will test ASPY in Binh Phuoc, Dak Nong, and Dak Lak, and ASMQ in Gia Lai. Two sites will be tested for iDES: Khanh Hoa (DHA-PPQ) and Lam Dong (DHA-PPQ). The implementors will be the National Institute of Malaria, Parasitology and Entomology/Institute for Malariaology, Parasitology and Entomology. Viet Nam identified the need for capacity-building in molecular training in Binh Phuoc and microscopy training in Dak Lak.
2.12 Partners’ comments

**ACTMalaria:** Ms Hugo expressed support for the TES network meeting and noted that the challenge of the spread of drug resistance remains. She encouraged countries to develop plans to have real QA strengthening for diagnostics – not only for microscopy but also for RDTs. She emphasized that expertise in microscopy should cascade from the national level to the lower levels. Confidence in diagnostics services should not rest on those at the national level, but on those delivering the services.

**Global Fund to Fight AIDS, Tuberculosis and Malaria:** Ms Gaviria emphasized that it is critical for GMS countries to demonstrate their progress towards elimination. To reach elimination, some of the GMS countries need to urgently change their drug regimens. She noted that the Global Fund is having its replenishment meeting in 2019 to decide on next steps for funding. Two key areas for high impact in Asia are tuberculosis and malaria elimination in the GMS. She encouraged countries to use the outcomes from the meeting to take action in progressing elimination, especially with regard to updating drug regimens.

**Clinton Health Access Initiative (CHAI):** Ms Ba commented on the delays experienced by countries when shifting drug regimens. She emphasized that closer collaboration between governments and partners can help accelerate that timeline. For example, CHAI can help provide support through trainings. She commented on other issues, including the challenges with stock-outs and access to hard-to-reach groups. Ms Ba thanked the Thailand programme for lessons learnt on how to operationalize guidance. Fostering cross-country collaboration is essential to improving the development of tools for case investigation and foci investigation.

**United States Agency for International Development (USAID)/President’s Malaria Initiative (PMI):** Dr Sintasath noted the support of USAID and PMI to the TES network meeting. He emphasized that the use of effective drugs is critical, and patients should not be receiving treatment with drugs that are failing. He noted the usefulness of the iDES model as the GMS moves to elimination. He also spoke on the issue raised by Dr Hongvanthong on the operationalization of policy treatment updates. There is an opportunity for donors and partners to help coordinate the next steps after a policy change is decided (e.g. drug arrival and delivery, registration and training). He further encouraged countries to have in-country discussions prior to and after attending the TES meeting, so that results can be sufficiently shared and evaluated.

**United Nations Office for Project Services (UNOPS):** Dr Molnar thanked the participants of the meeting and noted that UNOPS continues to support the implementation of elimination activities in the GMS.

**University of California, San Francisco (UCSF):** Ms Dantzer spoke on the opportunity for further engagement between research institutes, civil society organizations and partners to support follow-up and TES activities. She said that many implementation challenges are similar, such as lack of adherence and difficulties in locating patients. She noted that partners may be able to help identify and refer patients.

3. CONCLUSIONS, NEXT STEPS AND RECOMMENDATIONS

Dr Abeyasinghe thanked the Government of the Lao People’s Democratic Republic for kindly hosting the meeting. He also thanked the GMS country participants, the donors and partners for their comments and support.
He commented that the meeting was an important opportunity for in-depth discussions to help guide the GMS countries. He noted that the GMS now stands at a critical juncture. The Global Fund has made an unprecedented investment and there is strong political commitment, as evidenced by the recently signed *Ministerial Call for Action to Eliminate Malaria in the GMS before 2030*. Given the financial and political commitment, it is imperative that the GMS continue to progress towards elimination.

Dr Abeyasinghe emphasized that the GMS has the full support of WHO across multiple levels: six country offices, two regional offices, a subregional team based in Cambodia and WHO headquarters in Geneva. WHO continues to support countries in facilitating the generation of evidence and the development of recommendations, including updates to NTGs.

He noted the importance of national programmes taking ownership. There is a need to accelerate the decision-making process and to determine the areas where the maximum impact can be made.

### 3.1 Conclusions

**Overview of GMS malaria elimination:** GMS countries have achieved substantial progress towards malaria elimination, but significant transmission remains in some parts of Cambodia, the Lao People’s Democratic Republic, Myanmar and Viet Nam. The remaining challenges include: 1) sustainable financing; 2) project implementation in the remaining endemic areas and partnership coordination, 3) monitoring and addressing multidrug resistance, and 4) strengthening surveillance.

**Status of artemisinin resistance:** Artemisinin partial resistance alone does not affect the overall efficacy of ACTs if the partner drug remains effective. ACTs fail when parasites are resistant to the partner drug or to both artemisinin and the partner drug. In such cases, countries need to consider changing the first-line ACT.

**TES results:** Study results indicate that artemisinin partial resistance (presence of validated K13 mutants) and resistance to multiple partner drugs primarily affect the eastern part of the GMS (east of a vertical line drawn across Bangkok). In Cambodia, its adjacent provinces in the Lao People’s Democratic Republic, Viet Nam and Thailand showed high failure rates for DHA-PPQ) which is the first-line drug in Viet Nam and Thailand. In the Lao People’s Democratic Republic, the efficacy of AL as a first-line drug is also declining. In Cambodia, ASMQ and ASPY are efficacious, while the other countries are currently monitoring their efficacy. Based on the absence of the *P. falciparum* multidrug resistance 1 gene (pfmdr1) copy number prevalence, ASMQ should be efficacious in all countries listed. Myanmar data showed high efficacy rates (more than 90% for AL, DHA-PPQ, ASMQ and ASPY).

**Quality control monitoring:** Quality control monitoring is important to ensure the quality of TES and iDES implementation, with a focus on the clinical and laboratory (microscopy and PCR assays) outcomes, data validation, field coordination to facilitate patient enrolment, and regular on-site supervision to address field challenges. This monitoring allows for reliable data that can drive drug policy review/changes in a country.

**National treatment guidelines:** The GMS countries have different ACTs as first-line treatments. Most countries have quinine for seven days as a second-line treatment. However, the seven-day treatment with quinine is difficult to implement. All countries have low-dose PQ as a supplementary treatment for *P. falciparum*, but it is not yet operationalized in some countries. Training at health centres and in the community on the use and safety of low-dose PQ is crucial. All countries have PQ (14 days or 8 weeks) for radical cure of *P. vivax* in their national treatment guidelines. However, the
implementation of this policy has been slow. In addition to the selection of drugs, other issues are
critical to accelerate the elimination of malaria, such as universal access to prevention and treatment,
functional community treatment networks, drug management (adequate stocks of ACTs and rapid
diagnostic tests or RDTs in health centres and village malaria worker networks), and quality assurance
of ACTs. Although the use of triple combination therapy (e.g. DHA-PPQ plus mefloquine) has been
evaluated in some countries, the additional benefit (over ASMQ) is unclear if DHA-PPQ is no longer
effective.

Genetic markers: Results from molecular marker analyses in Cambodia, the Lao People’s
Democratic Republic, Myanmar and Viet Nam are largely in line with TES findings. Cambodia and
Viet Nam showed high resistance rates against artemisinin and PPQ, although Cambodia officially
decided to stop the use of DHA-PPQ around three years ago. There are no or very limited signs of
resistance against mefloquine and PYR. Results from the Lao People’s Democratic Republic did not
demonstrate signs of resistance for the samples investigated. Of note, there were no K13 mutants
detected in samples collected during the 2017 outbreak in Savannakhet. Results from Myanmar
showed some resistance to artemisinin, but not to partner drugs.

Transition to iDES: As countries approach elimination and malaria transmission declines,
strengthened surveillance systems can be used to collect and analyse data on drug efficacy. Through
iDES, countries can transition from using a sentinel surveillance system to relying on efficacy data
collected via the routine surveillance system. Thailand started piloting the feasibility of iDES in eight
provinces in 2017; China is planning a pilot for iDES for imported Pf and Pv cases.

3.2 Recommendations

3.2.1 Recommendations for Member States

Member States are encouraged to consider the following:

1) Continue monitoring the quality of TES implementation based on the WHO quality control
checklist.
2) Continue efforts to strengthen microscopy quality assurance for TES and elimination
purposes.
3) Review the results of TES within countries; consider switching the first-line drug, if the first-
line drug is no longer effective nationally or sub-nationally.
4) Identify alternative ACT as second-line treatment, based on the TES results, and discontinue
the use of quinine.
5) Accelerate the roll-out of glucose-6-phosphate dehydrogenase (G6PD) point-of-care (POC)
tests (or other measures such as close monitoring) to enable the radical cure of *P. vivax* with
primaquine.
6) Accelerate the registration process of all ACTs and test alternative ACTs in the TES.
7) Review and consider implementation of relevant recommendations from 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
(Phnom Penh, Cambodia, 26–28 February 2018).

3.2.2 Recommendations for WHO

WHO is requested to consider the following:

1) Share the latest TES template with all GMS countries.
2) Continue providing support for countries moving into elimination settings, particularly as they transition to iDES, including the finalization of the iDES protocol.

3) Review and revise national treatment guidelines based on available TES data and other information.

4) Support the full operationalization of revised national treatment guidelines with national programmes and partners, including low single dose of primaquine for *P. falciparum* infections.
## AGENDA

### Day 1: Thursday, 27 September 2018

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
<th>Presenter(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>08:00 – 08:30</td>
<td>Registration</td>
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</tr>
<tr>
<td>8:30 – 09:30</td>
<td><strong>Opening Session</strong></td>
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</tr>
<tr>
<td>8:30 – 09:30</td>
<td>Welcome address</td>
<td>Dr Juliet Anne Fleischl, WHO Representative Lao PDR (on behalf of the Regional Director, WHO Western Pacific Region) Dr Somphone Soulaphy, Chief, Division for Diseases Control, CDC/MOH</td>
</tr>
<tr>
<td></td>
<td>Meeting objectives</td>
<td>Dr Rabindra Abeyasinghe</td>
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<tr>
<td></td>
<td>Self-introduction of participants and observers</td>
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<tr>
<td></td>
<td>Nomination of the Chair and Rapporteur</td>
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<tr>
<td></td>
<td>Administrative announcements</td>
<td>Dr Maria Dorina Bustos, Malaria Technical Officer</td>
</tr>
<tr>
<td>09:30 -10:00</td>
<td><strong>Group photograph followed by coffee/tea break</strong></td>
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<tr>
<td>10:00 –10:15</td>
<td><strong>Session 1:</strong> Regional updates</td>
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<tr>
<td>10:00 –10:15</td>
<td>Review of recommendations 2017 and progress</td>
<td>Dr Maria Dorina Bustos</td>
</tr>
<tr>
<td>10:15 –10:45</td>
<td>Updates on anti-malarial drug resistance including partial resistance to artemisinins and partner drugs in the Greater Mekong Subregion</td>
<td>Dr Pascal Ringwald, Coordinator, Drug Efficacy and Response, Global Malaria Programme</td>
</tr>
<tr>
<td>10:45 –11:15</td>
<td>Strengthening coordination and partnerships to accelerate elimination in the GMS</td>
<td>Dr Hiromasa Okayasu, Coordinator, Mekong Malaria Elimination (MME) Program</td>
</tr>
<tr>
<td>11:15 –11:45</td>
<td>Monitoring drug efficacy: from TES to integrating drug efficacy surveillance (iDES) into routine surveillance system in areas pursuing malaria elimination</td>
<td>Dr Pascal Ringwald</td>
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<tr>
<td>11:45 –12:00</td>
<td>Plenary Discussion</td>
<td></td>
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<tr>
<td>12:00 –13:00</td>
<td><strong>Lunch break</strong></td>
<td></td>
</tr>
<tr>
<td>13:00 –14:30</td>
<td><strong>Session 2:</strong> Country Presentations from Greater Mekong Subregion TES (15 min country presentation, followed by discussion)</td>
<td></td>
</tr>
<tr>
<td>13:00 –14:30</td>
<td>Cambodia</td>
<td>CNM TES Principal Investigator</td>
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<td></td>
<td>Lao PDR</td>
<td>CMPE TES Principal Investigator</td>
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<tr>
<td></td>
<td>Myanmar</td>
<td>DMR TES principal Investigator</td>
</tr>
<tr>
<td></td>
<td>Viet Nam</td>
<td>NIMPE TES Principal Investigator</td>
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<tr>
<td>14:30–15:00</td>
<td><strong>Coffee / tea break</strong></td>
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### Session 3: Integrated drug efficacy surveillance and QC in TES implementation

<table>
<thead>
<tr>
<th>Time</th>
<th>Location</th>
<th>Speaker/Investigator</th>
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</thead>
<tbody>
<tr>
<td>15:00 – 17:00</td>
<td>Yunnan, China</td>
<td>NIPD Principal Investigator</td>
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<td></td>
<td>Thailand (pilot implementation of iDES)</td>
<td>BVBD Principal Investigator</td>
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<td></td>
<td>Quality Control in TES and iDES: implementation challenges</td>
<td>Dr Maria Dorina Bustos</td>
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</tbody>
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<thead>
<tr>
<th>Time</th>
<th>Event</th>
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<tbody>
<tr>
<td>18:00 – 19:30</td>
<td>Reception dinner (Hotel venue)</td>
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### Day 2: Friday, 28 September 2018

#### Session 4: Updates on antimalarial resistance and molecular markers

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Speaker/Speaker/Investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>08:30 – 09:00</td>
<td>Summary of country results (GMS countries)</td>
<td>Dr Pascal Ringwald</td>
</tr>
<tr>
<td>09:00 - 09:45</td>
<td>Updates from the malaria program managers’ meeting of malaria endemic countries of WPR in relation to drug policy implementation – Q &amp; A</td>
<td>Dr Rabindra Abeyasinghe</td>
</tr>
<tr>
<td>09:45 – 10:15</td>
<td>Updates on Kelch 13, Plasmepsin and other molecular markers for resistance in the GMS – Q&amp;A</td>
<td>Dr Benoit Witkowski, Institute Pasteur Cambodia</td>
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<tr>
<td>10:15 -10:45</td>
<td>Coffee/tea break</td>
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#### Session 5: Planning and budget: TES, TES + MM, integrated monitoring drug efficacy in surveillance

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<tr>
<th>Time</th>
<th>Event</th>
<th>Speaker/Investigator</th>
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<tbody>
<tr>
<td>10:45 – 12:00</td>
<td>Introduction to Group Work • Country breakout groups: 2019-20 country TES or iDES plans and budgets</td>
<td>Dr Maria Dorina Bustos Facilitators (WHO staff)</td>
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<tr>
<td>12:00 -13:00</td>
<td>Lunch break</td>
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<tr>
<td>13:00 – 14:00</td>
<td>Group Work continued</td>
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</table>

#### Session 6: Presentation of GMS Country plans

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Country TES Principal Investigators</th>
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<tbody>
<tr>
<td>14:00- 15:30</td>
<td>Plenary presentations and discussion of country plans / drug resistance surveillance and budget (10 mins / country); Q &amp; A</td>
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<td>- Cambodia</td>
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<td>- Lao People's Democratic Republic</td>
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<td></td>
<td>- Myanmar</td>
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<td></td>
<td>- Viet Nam</td>
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<tr>
<td></td>
<td>- China (Yunnan)</td>
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<tr>
<td></td>
<td>- Thailand</td>
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<tr>
<td>15:30 -16:00</td>
<td>Coffee/tea break</td>
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<tr>
<td>16:00 – 16:30</td>
<td>Partners’ comments: ACTMalaria, BMGF, CHAI, GFATM, USAID/PMI, UCSF, UNOPS</td>
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#### Session 7: Next Steps & closing

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<tr>
<th>Time</th>
<th>Event</th>
<th>Speaker/Investigator</th>
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<tbody>
<tr>
<td>16:30 – 16:45</td>
<td>Conclusion, next steps and recommendations</td>
<td>Dr Rabindra Abeyasinghe, Dr Pascal Ringwald</td>
</tr>
<tr>
<td>16:45 – 17:00</td>
<td>Closing</td>
<td>Dr Hiro Okayasu</td>
</tr>
</tbody>
</table>
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## Efficacy of ACTs for *P. falciparum* malaria

<table>
<thead>
<tr>
<th>Country</th>
<th>Efficacious</th>
<th>Failing</th>
<th>PQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cambodia</td>
<td>ASMQ, ASPY (east), AL (borderline)</td>
<td>DHA-PPQ, ASAQ, ASPY (west)</td>
<td>✓</td>
</tr>
<tr>
<td>Lao People’s Democratic Republic</td>
<td>ASMQ (MM)</td>
<td>AL, (small sample size) DHA-PPQ</td>
<td>✓</td>
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<tr>
<td>Myanmar</td>
<td>AL, ASMQ, DHA-PPQ, ASPY, ASAQ (old data)</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Thailand</td>
<td>DHA-PPQ (west), ASMQ (east), ASPY, AL (borderline)</td>
<td>DHA-PPQ (east), ASMQ (west)</td>
<td>✓</td>
</tr>
<tr>
<td>Viet Nam</td>
<td>DHA-PPQ, ASPY, ASMQ (MM), ASAQ (old data)</td>
<td>DHA-PPQ (at least 2 provinces)</td>
<td>✓</td>
</tr>
</tbody>
</table>