NINTH MEETING OF THE GREATER MEKONG SUBREGION THERAPEUTIC EFFICACY STUDY NETWORK

15–16 September 2021
Virtual meeting
MEETING REPORT

NINTH MEETING OF THE GREATER MEKONG SUBREGION
THERAPEUTIC EFFICACY STUDY NETWORK

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NOTE

The views expressed in this report are those of the participants of the Ninth Meeting of the Greater Mekong Subregion Therapeutic Efficacy Study 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 virtual Ninth Meeting of the Greater Mekong Subregion Therapeutic Efficacy Study Network from 15 to 16 September 2021.
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KEYWORDS

Antimalarials – therapeutic use / Drug resistance / Malaria-prevention and control / Mekong valley
ABBREVIATIONS

ACPR adequate clinical and parasitological response
ACT artemisinin-based combination therapy
AFRIMS Armed Forces Research Institute of Medical Sciences
AL artemether-lumefantrine
AQ amodiaquine
AS-AQ artesunate-amodiaquine
AS-MQ artesunate-mefloquine
AS-PPQ artesunate-piperaquine
AS-PY artesunate-pyronaridine
AS+SP artesunate+sulfadoxine-pyrimethamine
eCDS electronic Communicable Disease System
CMPE Center for Malaria, Parasitology, and Entomology (Lao People’s Democratic Republic)
CNM National Center for Parasitology, Entomology and Malaria Control (Cambodia)
COVID-19 coronavirus disease 2019
CQ chloroquine
DHA-PPQ dihydroartemisinin-piperaquine
DHIS District Health Information System
DVBD Division for Vector Borne Diseases (Thailand)
ECAMM External Competency Assessment of Malaria Microscopists
EQA external quality assessment
ERC Ethics Review Committee
G6PD glucose-6-phosphate dehydrogenase
glurp glutamate-rich protein
GMS Greater Mekong Subregion
HRP histidine-rich protein
iDES integrated drug efficacy surveillance
IMPE Institute of Malariology Parasitology and Entomology Quy Nhon (Viet Nam)
IPT intermittent preventive treatment
K13 Kelch 13
LLIHN long-lasting insecticidal hammock net
LLIN long-lasting insecticidal net
MME Mekong Malaria Elimination programme
MMS malaria management system
MORU Mahidol-Oxford Research Unit
msp merozoite surface proteins
NIMPE National Institute of Malariology, Parasitology and Entomology (Viet Nam)
NIPD National Institute of Parasitic Diseases (China)
NMCP National Malaria Control Programme (Myanmar)
NMP national malaria programme
NRA national regulatory agency
NTG national treatment guideline
PCR polymerase chain reaction
<table>
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<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>pLDH</td>
<td>parasite lactate dehydrogenase</td>
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<td>PMI</td>
<td>U.S. President's Malaria Initiative</td>
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<td>PPQ</td>
<td>piperaquine</td>
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<tr>
<td>PQ</td>
<td>primaquine</td>
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<tr>
<td>PY</td>
<td>pyronaridine</td>
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<tr>
<td>QA</td>
<td>quality assurance</td>
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<td>QC</td>
<td>quality control</td>
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<tr>
<td>RAI</td>
<td>Regional Artemisinin-resistance Initiative</td>
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<tr>
<td>RDT</td>
<td>rapid diagnostic test</td>
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<td>RSC</td>
<td>Regional Steering Committee</td>
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<tr>
<td>SOP</td>
<td>standard operating procedure</td>
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<td>TDA</td>
<td>targeted drug administration</td>
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<td>TES</td>
<td>therapeutic efficacy studies</td>
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<td>TQ</td>
<td>tafenoquine</td>
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<tr>
<td>UNOPS</td>
<td>United Nations Office for Project Services</td>
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On 15 and 16 September 2021, the World Health Organization (WHO) Mekong Malaria Elimination (MME) programme hosted the virtual Ninth Meeting of the Greater Mekong Subregion Therapeutic Efficacy Studies Network with representatives from national malaria programmes (NMPs), focal points from Greater Mekong Subregion (GMS) countries, as well as technical experts and partners. Representatives from the GMS Member States – Cambodia, China, the Lao People's Democratic Republic, Myanmar, Thailand and Viet Nam – attended the workshop to monitor the results of therapeutic efficacy studies (TES) and integrated drug efficacy surveillance (iDES) from the past year, review the efficacy of antimalarial drugs, identify alternative artemisinin-based combination therapies (ACTs) to revise of national treatment guidelines (NTGs) and prioritize future needs of the countries, as necessary.

The main discussion points included the results of recent TES and iDES, future priorities and activities given the present results, ways to continue monitoring drug efficacy in malaria-free and near elimination settings, the risk of *Plasmodium falciparum* histidine-rich protein 2 (pfHRP2) and pfHRP3 deletions and the effective management and monitoring of *P. vivax* malaria in the GMS.

The key conclusions of the meeting included:

- **Overview of GMS malaria elimination:** From January to July 2021, the GMS countries recorded a 26% reduction in malaria cases compared to the same period in 2020. At the same time, *P. falciparum* + mixed cases fell by 55%, and *P. vivax* cases dropped by 19%.

- **Drug efficacy:** In 2021, quality TES and monitoring were completed in four GMS countries: Cambodia, the Lao People’s Democratic Republic, Myanmar and Viet Nam. As malaria case numbers continue to drop, iDES continues to be implemented nationwide in Thailand and rolled out in Viet Nam and the Lao People's Democratic Republic. Cambodia started an iDES pilot in three districts in one province. While artesunate-pyronaridine (AS-PY) is registered as an alternative ACT and a second-line drug, its use is limited in Cambodia and the Lao People’s Democratic Republic due to supply issues.
  - **Cambodia:** Artesunate-mefloquine (AS-MQ) and AS-PY continue to demonstrate efficacy for *P. falciparum* and *P. vivax* malaria. In 2020, TES indicated that the efficacy of AS-MQ remains high.
  - **Lao People’s Democratic Republic:** AS-MQ and AS-PY remain efficacious. Data on artemether-lumefantrine (AL) from 2019-2020 show high efficacy compared to 2018 against *P. falciparum* and *P. vivax* malaria with a larger sample size than was achieved in 2018. Molecular data indicated fewer K13 mutations compared to 2018 except in Champassak province, there is mefloquine sensitivity in all samples assayed, and plasmepsin2 copy number is decreasing, showing a reversal of piperaquine (PPQ) resistance.
  - **Myanmar:** AL, AS-PY and dihydroartemisinin-piperaquine (DHA-PPQ) remain efficacious. Similarly, chloroquine (CQ) for *P. vivax* cases also remains efficacious.
  - **Viet Nam:** AS-PY and AS-MQ are efficacious. In September 2020, treatment failures with DHA-PPQ led to two additional provinces (Phu Yen and Khanh Hoa) switching to AS-PY. Molecular data indicate PPQ resistance along the provinces bordering Cambodia.
  - **Thailand:** DHA-PPQ for *P. falciparum* cases is efficacious where data is available, except in Sisaket province, bordering Cambodia, where AS-PY is the first-line treatment. CQ + primaquine (PQ) for *P. vivax* cases also remain efficacious.
• **Quality control in TES and iDES:** Adherence to WHO’s quality assurance (QA) and quality control (QC) protocols are mandatory. Common deviations should be noted to avoid incorrect or missing information. QA and QC were maintained through regular monitoring and communications between WHO country staff, NMP investigators and the WHO regional drug resistance monitor despite pandemic restrictions.

• **Efficacy monitoring in a malaria-free setting:** iDES is feasible as a routine activity in a “prevention of reestablishment” setting. The continuous training of relevant health staff, particularly in microscopy, is essential to ensure the effectiveness of iDES among imported cases.

• **pfHRP2/3 deletions:** Histidine-rich protein 2 (HRP2) is a protein expressed only by *P. falciparum* and is the target for the most used rapid diagnostic tests (RDTs). HRP2 RDTs generally have the highest sensitivity of the RDTs for *P. falciparum* malaria. However, parasite strains in several countries have been identified that have deletions in the genes encoding HRP2 or the similar HRP3 protein. Studies done in the past on the Myanmar-China border detected the presence of parasites with pfHRP2/3 deletions. Surveys and studies are needed to map the prevalence and impact of pfHRP2/3 deletions in the subregion. NMPs should keep note of anecdotal evidence or formal complaints regarding false-negative RDTs as this may indicate the presence of pfHRP2/3 deletions.

• **Effective management and monitoring of *P. vivax* malaria:** The efficacy of drugs for treating *P. vivax* in the GMS ranges from 94.7% to 100%. But there are challenges in the 14-day PQ radical treatment and monitoring for relapse or reinfection beyond day 28/42 in iDES. Routine TES for *P. vivax* infections looks at efficacy and resistance to the treatment of the asexual blood stages parasites.

• **Supervised treatments:** Supervised treatment is required for TES and iDES. In iDES, countries are adapting to local conditions to find ways of assuring that the treatment is taken. The first dose of treatment under iDES is always supervised by health staff; documentation for patients taking subsequent doses is sometimes inadequate. If iDES shows high numbers of treatment failures, confirmatory studies should be done and a change in first-line treatment should be considered.
1. INTRODUCTION

1.1 Background

The World Health Organization (WHO) has been hosting meetings of the Greater Mekong Subregion (GMS) Therapeutic Efficacy Studies (TES) Network since 2008 to support countries in reviewing drug efficacy data and developing country-specific plans for efficacy monitoring. GMS countries continue to use TES as the gold standard for monitoring drug efficacy. As more countries enter the malaria elimination phase, they have started implementing integrated drug efficacy surveillance (iDES).

The Ministerial Call for Action to Eliminate Malaria in the GMS before 2030, signed by GMS ministers of health in 2018, acknowledged that multidrug resistance is a serious concern for regional and international health security, requiring immediate implementation of the *WHO Strategy for Malaria Elimination in the GMS (2015–2030)*. The World Health Organization (WHO) supports the implementation of this strategy across multiple levels: six GMS country offices, two regional offices (South-East Asia and the Western Pacific), the subregional team of the Mekong Malaria Elimination (MME) programme and the Global Malaria Programme at WHO headquarters.

1.2 Meeting objectives

The objectives of the meeting were:

**General objective**
1) to review available results from the ongoing TES and iDES and develop action plans for the next two years;

**Specific objectives**
1) to present the results of the recent TES and iDES in line with recommendations from the last meeting;
2) to present the trends of *Kelch 13* (K13), the molecular marker for tracking artemisinin resistance, and of other molecular markers for monitoring malaria drug resistance;
3) to assess the impact of the coronavirus disease 2019 (COVID-19) pandemic on TES and iDES and identify risk mitigation measures; and
4) to develop GMS and country workplans and budgets for TES and iDES implementation and monitoring for 2022–2023.

2. PROCEEDINGS

2.1 Opening session of day 1

Dr Li Ailan, WHO Representative (Cambodia), delivered the welcome address to the meeting participants. Following this, Dr Pascal Ringwald, Coordinator, Director’s Office from WHO’s Global Malaria Programme, delivered the opening remarks. Dr Luciano Tuseo, Coordinator of WHO’s MME programme, presented the meeting objectives. This was followed by the nomination of Professor Tran Thanh Duong, Director, National Institute of Malariology, Parasitology and Entomology (NIMPE), Viet Nam, as chairperson for the first day of the meeting. Dr Maria Dorina Bustos, Technical Officer, WHO Regional Office for South-East Asia, provided an administrative announcement. Professor Tran accepted the nomination and opened the conference.
2.2 Review of recommendations from 2020 and progress

Dr Maria Dorina Bustos, Technical Officer from the WHO Regional Office for South-East Asia, reviewed the recommendations for GMS countries and WHO from the Eighth Meeting of the GMS TES Network in 2020. Member States were encouraged to consider the following:

1) Continue monitoring the quality of TES implementation based on the WHO quality control (QC) checklist while ensuring proper front-line workers safety in the context of the COVID-19 pandemic.
2) Continue efforts to strengthen quality assurance (QA) for microscopy and molecular assays for achieving elimination.
3) Review the results of TES within countries and consider switching the first-line drug if it is no longer effective nationally rather than subnationally.
4) National malaria programmes (NMPs) should continue to work with national regulatory agencies (NRAs) to identify and resolve bottlenecks to accelerate the registration process of antimalarials, as well as post-marketing surveillance for quality and safety.
5) Continue to refine and roll out iDES, where feasible.
6) Ensure integration of iDES with procedures to measure molecular markers.
7) Integrate laboratory microscopy into iDES.
8) In the context of the COVID-19 pandemic, test suspected cases as per national guidelines, ensuring safety and compliance with infection prevention and control measures of the patients and the health staff.
9) Strengthen the core structures and systems for malaria as a central element of the COVID-19 pandemic response.
10) Continue to strengthen microscopy capacity during the COVID-19 pandemic using innovative methods such as the virtual External Competency Assessment of Malaria Microscopists (ECAMM).
11) Artesunate-mefloquine (AS-MQ) efficacy is very good in Cambodia, but this needs to be monitored. If it continues to be successful, it could be considered a relevant option for countries with KEL1/PLA1 circulation. The situation should be closely monitored in Viet Nam after the full implementation of artesunate-pyronaridine (AS-PY) with regards to KEL1/PLA1.
12) There is now a narrow operational window to eliminate malaria. AS-MQ and AS-PY display promising efficacy in several countries and could be used as first- and/or second-line drugs in areas of multidrug resistance.

Following the review, Dr Bustos provided updates on the progress since the last meeting. In 2021, quality TES and monitoring exercises were completed in four GMS countries: Cambodia, the Lao People’s Democratic Republic, Myanmar and Viet Nam. ECAMM was not conducted in any country in the past year. However, WHO extended the validity of certificates needed for microscopy for one year until December 2021. Eight national malaria laboratories from Viet Nam (3), Myanmar (1), Cambodia (1), China (1), the Lao People’s Democratic Republic (1) and Thailand (1) participated in the tenth WHO regional external quality assessment (EQA) of malaria labs.

WHO continues to support the full operationalization of revised national treatment guidelines (NTGs) with NMPs and partners. NTGs continue to be updated across the GMS. In Viet Nam, dihydroartemisinin-piperazine (DHA-PPQ) is used as a first-line drug. The country recently revised its NTGs to use AS-PY as a first-line drug (as well as AS-MQ) in six provinces with more than a 10% failure rate to DHA-PPQ. Quinine + doxycycline/clindamycin are the second-line drugs for artemisinin-based combination therapy (ACT) treatment failure. Cambodia’s NTGs were also revised to utilize quinine + tetracycline as a second-line drug.

WHO has provided support to pilot and expand iDES in the GMS. The Lao People’s Democratic Republic piloted iDES in two provinces and is now expanding it to 120 elimination districts. Thailand
continued to implement iDES nationwide. Additionally, Viet Nam piloted iDES in one province and expanded across six communes in three provinces.

AS-MQ efficacy in Cambodia is stable. It continues to be used as the first-line drug, with AS-PY registered as the second-line drug. AS-MQ is also registered as the second-line drug in the Lao People’s Democratic Republic. AS-PY is used as a first-line drug in two provinces in Thailand, while other provinces utilize it as a second-line drug.

In terms of procurement, the use of AS-PY as a second-line drug in Cambodia is limited due to supply issues. The Lao People’s Democratic Republic has procured AS-MQ as its second-line drug. Viet Nam has procured AS-PY as its second-line drug and is using it in six provinces with >10% failure to DHA-PPQ. It also uses AS-MQ as a second-line drug, but it is not available locally.

2.3 Overview of the Mekong Malaria Elimination programme in the Greater Mekong Subregion

Dr Luciano Tuseo, Coordinator of the WHO MME programme, presented the status of malaria and COVID-19 in the GMS since the last TES meeting. The country targets for malaria elimination in the GMS include the elimination of \( P. \text{ falciparum} \) malaria by 2023 and the elimination of all species of human malaria by 2030 (Thailand and Cambodia have set elimination targets for 2024 and 2025, respectively). He highlighted that China was declared malaria-free on 30 June 2021, and Thailand was accepted into WHO’s E-2025 initiative to eliminate malaria by 2025.

The GMS continues to experience a decrease in malaria cases and deaths. The GMS has observed a 26% reduction of total cases by July 2021 when compared to the same period in 2020. At the same time, \( P. \text{ falciparum} + \) mixed cases have been reduced by 55%. Similarly, \( P. \text{ vivax} \) cases fell by 19% in the first seven months of 2021 compared to 2020. There was a 35% decrease in tested cases due to the ongoing COVID-19 pandemic. It should be noted that reporting completeness from Myanmar has declined since February 2021.

From January to July 2021, Cambodia recorded a 76% reduction of \( P. \text{ falciparum} + \) mixed cases and a 70% reduction of \( P. \text{ vivax} \) cases when compared to the same period in 2020. The Lao People’s Democratic Republic recorded a 58% increase of \( P. \text{ falciparum} + \) mixed cases and a 15% increase in \( P. \text{ vivax} \) cases. At the same time, Thailand saw a 74% reduction of \( P. \text{ falciparum} + \) mixed cases and a 36% reduction of \( P. \text{ vivax} \) cases. Viet Nam’s data show an 81% reduction of \( P. \text{ falciparum} + \) mixed cases and a 61% reduction of \( P. \text{ vivax} \) cases. In Myanmar, the political situation impacts all malaria activities, and malaria control is now a priority. Dr Tuseo noted that the transmission of COVID-19 continues to impact malaria activities in the GMS. COVID-19 cases are increasing across the GMS, although vaccine roll-outs are well underway in all countries. Despite the presence of COVID-19, stocks of rapid diagnostic tests (RDTs) and ACTs are sufficient.

Dr Tuseo also outlined the status of focalized innovative approaches (including targeted drug administration (TDA) and intermittent preventive treatment (IPT)), which have now started in Cambodia and the Lao People’s Democratic Republic. Cambodia’s focalized innovative approaches now cover 65% of the target villages. Similar interventions are also under discussion in Viet Nam.

2.4 Plenary discussion

During the discussion session, Dr Faisal Mansoor, Head of Programme Unit, United Nations Office for Project Services (UNOPS), noted that the Global Fund to Fight AIDS, Tuberculosis and Malaria has now approved more than US$ 100 million worth of support for malaria and COVID-19 support in Myanmar. He acknowledged that the political situation in the country since February 2021 had stalled work with governmental partners, but activities continue through volunteers and nongovernmental organizations. Despite a stall in malaria supplies in March 2021, there have not been any stock-outs, and supply issues were mitigated. There were increased requests for primaquine (PQ) due to population
movements to endemic areas, resulting in more *P. vivax* cases. Overall, this situation has heavily impacted elimination activities as the focus is shifting to cover areas unserved by the public system.

Dr Khin Lin, representative from the National Malaria Control Programme (NMCP), Myanmar, provided an update on the COVID-19 vaccination status in Myanmar. He noted that 50% of the population is expected to be vaccinated by the end of 2021.

Dr Sovannaroth Siv, representative from the National Center for Parasitology, Entomology and Malaria Control (CNM) of Cambodia, confirmed Dr Tuseo’s update on the country’s malaria and COVID-19 situation.

Dr Keobouphaphone Chindavongsa, representative from the Center for Malaria, Parasitology, and Entomology (CMPE), Lao People's Democratic Republic, noted the increases in *P. falciparum* and *P. vivax* cases were recorded in focalized areas in two districts and were linked to the fact that the wet season started earlier this year than in 2020. Weekly reporting in these areas facilitated rapid outbreak responses with intensive reactive case detection that has reduced transmission in these areas.

Dr Rungniran Sugaram, representative from the Division for Vector Borne Diseases (DVBD), Thailand, highlighted that COVID-19 cases are currently concentrated in Bangkok and border areas with Myanmar. Over the coming months, Thailand will need to mitigate the impact of rising *P. vivax* cases reported in the border areas and ensure stable procurement processes.

Associate Professor Dr Bui Quang Phuc, representative from NIMPE, Viet Nam, outlined that malaria interventions were limited in the COVID-19 context. In 2021, Viet Nam has recorded only 2095 malaria cases, of which the majority are *P. vivax*. He also mentioned that TES are currently suspended due to the COVID-19 outbreaks in Viet Nam’s south and central provinces.

### 2.5 Updates from Greater Mekong Subregion countries on the results and priorities of therapeutic efficacy studies and integrated drug efficacy surveillance

#### 2.5.1 Cambodia

Dr Leang Rithea, TES Principal Investigator from Cambodia’s CNM, provided an update on the country’s progress in TES and iDES. The last revision in Cambodia’s NTGs occurred in 2016 when the country shifted from DHA-PPQ to AS-MQ. The current malaria policy for uncomplicated malaria is AS-MQ for the first-line treatment and AS-PY for the second-line treatment.

In 2020, the CNM completed TES for AS-PY for *P. falciparum* and *P. vivax* cases in Kampong Speu and Stung Treng and for AS-MQ in Kampong Speu, Pursat and Ratanakiri. The TES found that the efficacy of AS-MQ and AS-PY for *P. falciparum* cases through adequate clinical and parasitological response (ACPR) was 100% in all study sites. In terms of *P. vivax* cases, AS-MQ was 100% efficacious in all study sites. AS-PY was 100% efficacious in Stung Treng and 98.3% efficacious in Kampong Speu.

In 2021, the CNM will complete TES for AS-MQ in *P. falciparum* and *P. vivax* cases from August to December. The four study sites are based in Stung Treng, Kampong Speu and Ratanakiri. Due to low case numbers, the CNM has recruited patients from nearby health centres. Despite the delays in this year’s TES implementation, training for drug monitoring was conducted in September 2021.

Less than 5% of patients report side-effects from AS-MQ. He also noted that Cambodia’s experience highlights the importance of acquiring high-quality microscopes in laboratories for reading the blood slides required for iDES. Monitoring and evaluation activities remain central to ensuring that health centres collect the correct data needed for TES and iDES. The CNM is looking to procure AS-PY as a
second-line drug. However, there have been issues in procuring enough supplies to utilize it as a second-line drug.

In response to queries regarding iDES, Dr Siv mentioned that Cambodia initiated an iDES pilot in three districts in one province but encountered operational challenges with district health centre staff and village volunteers for follow-up, despite financial support through external sources. The CNM is currently seeking to outsource iDES implementation through third parties to support its operation and provide performance-based incentives for follow-up visits. Some reservations were raised by WHO about the sustainability of such an approach rather than using the existing elimination surveillance systems in the districts/provinces with simple standard operating procedures (SOPs) and iDES training and supervision of health centre staff and volunteers.

2.5.2 Lao People's Democratic Republic

Dr Keobouphaphone Chindavongsa, TES principal investigator from the Lao People's Democratic Republic’s CMPE, delivered a presentation on the country’s malaria elimination progress. In 2021, malaria cases were concentrated in the southern part of the Lao People's Democratic Republic. From 2019 to 2020, the CMPE conducted TES for artemether-lumefantrine (AL) in the three southern provinces of Champasak, Salavan, and Savannakhet. AL demonstrated 96.3% efficacy for *P. falciparum* cases and 100% for *P. vivax* cases in Savannakhet, whereas in Champasak and Salavan, AL demonstrated 100% efficacy for both *P. falciparum* and *P. vivax* cases. Therefore, AL TES results from 2020 indicate its continued effectiveness for treating *P. falciparum* and *P. vivax* malaria. In 2021, the WHO Ethics Review Committee (ERC) approved TES for *P. falciparum* and *P. vivax* in three sites in Savannakhet, Sekong, and Attopue. However, COVID-19 restrictions led to delays in the implementation of the TES planned for 2021.

Molecular markers indicate that K13 mutations have continued to decline on day zero, and there is a limited number of C580Y except in Champassak province. This suggests artemisinin resistance is waning. The molecular marker data showed that there were no indicators of mefloquine resistance. Plasmepsin2 copy number is also decreasing, indicating a reversal of piperaquine (PPQ) resistance.

From 2019 to 2021, iDES were piloted in Luang Prabang and Phongsaly. ACPR results from the 17 cases showed 100% efficacy. The CMPE has not recruited any cases in 2021.

One of the major challenges for TES relates to the lower number of malaria cases in study sites. Most cases detected at the health centre and village levels are located in remote areas where referral for recruitment is not always successful. Another challenge experienced over the past year was the COVID-19 movement restrictions, resulting in delays among trained and qualified staff to conduct microscopy QA.

The TES and iDES findings were used to inform national registration of antimalarials in the *List of Essential Medicines*. The current malaria policy for uncomplicated *P. falciparum* malaria cases is AL + PQ for the first-line treatment. AS-MQ + a single low dose of PQ recently replaced quinine as the second-line treatment. Uncomplicated *P. vivax* malaria cases receive AL + PQ (14 days) with a glucose-6-phosphate dehydrogenase (G6PD) test. For the second-line treatment, the NTG policy changed from an oral dose of chloroquine (CQ) + PQ with a G6PD test to AS-MQ + PQ (14 days) with a G6PD test.

AS-MQ was piloted as the TDA policy under the ongoing “accelerated” strategies. However, the side-effects of AS-MQ have resulted in the absence or refusal of patients during follow-up dosages. As a result, the CMPE has recently reactivated a task force on malaria diagnosis and treatment to decide whether AS-MQ or AS-PY should be selected for TDA.

Dr Keobouphaphone outlined that the CMPE identified the need for further studies to strengthen the integration of iDES into existing malaria elimination surveillance. The research should include the collection of molecular data on *P. vivax* cases at day 28 and day 90 of treatment. Further work is also needed to develop SOPs, monitoring forms and training materials to track the compliance of *P. vivax* cases on 14-day radical treatment.
In 2022, the CMPE will focus on strengthening QA/QC, monitoring artemisinin resistance and monitoring the efficacy of AL. iDES will be scaled up to cover 121 of 148 districts in the country. Discussions have begun about potentially conducting AS-MQ and AS-PY efficacy studies.

The CMPE performs QC through monitoring and field supervision activities that are managed by central and external teams. Microscopy QA is provided by WHO-certified microscopists based in the provinces or CMPE. Final data validation is jointly conducted by the CMPE and WHO. Challenges in QC include the limited availability of certified microscopists at the subnational level. Project staff report heavy workloads, which limit the time to perform routine monitoring. COVID-19 outbreaks in TES sites have also delayed QA processes.

2.5.3 Myanmar

Dr Moe Kyaw Myint, TES principal investigator, presented the TES results for Myanmar. In 2019, AL and DHA-PPQ for P. falciparum were investigated in Tamu, Sagaing State. AL indicated 96.7% efficacy, while DHA-PPQ demonstrated 100% efficacy. In 2020, TES in Buthidaung, Rakhine State investigated AL and DHA-PPQ in P. falciparum cases as well as CQ in P. vivax cases. The ACPR findings indicate full efficacy for AL, as well as 98% efficacy for DHA-PPQ. The results of TES for CQ in P. vivax cases show 96% efficacy.

In 2021, TES were approved for CQ in Myawaddy in Kayin State, Homalin in Sagaing Region and Kawthaung in Tanintharyi Region. TES for AL are planned for Homalin and Kawthaung. DHA-PPQ will be studied in Moemeik, Northern Shan State. The implementation of these TES is pending.

The current malaria policy for uncomplicated P. falciparum malaria cases is AL for three days + PQ at day zero with the first dose of AL. For treatment failure within 28 days, patients are prescribed an alternate ACT + PQ. For treatment failure after 28 days, patients are prescribed AL + PQ. Pregnant P. falciparum malaria cases receive an oral dose of quinine and clindamycin for seven days in the first trimester and AL for three days in the second and third trimesters. Mixed malaria cases receive AL for three days + PQ for 14 days. The treatment of uncomplicated non-P. vivax malaria is CQ + PQ for 14 days for all levels. PQ is not given for P. malariae.

Dr Moe Kyaw Myint described the key challenges, including security concerns in many aspects of TES implementation, travel restrictions that affect the whole country and a shortage of clinical experts and technical staff. The remote location of malaria cases has posed a challenge for completing TES. Overall, TES indicate that the current ACTs are working, but given the current political situation, the ability to effectively implement TES and visit study sites is limited.

2.5.4 Viet Nam

Associate Professor Dr Bui Quang Phuc, TES principal investigator from the NIMPE, presented the TES findings for Viet Nam. The TES results from 2020 indicate full ACPR efficacy of AS-MQ for P. falciparum in Gia Lai and Dak Lak, as well as full efficacy of AS-PY in Dak Nong. In 2021, TES of AS-PY for P. falciparum cases are ongoing in Binh Phuoc, Gia Lai and Phu Yen. For P. vivax, CQ TES are ongoing in Binh Phuoc, Gia Lai and Phu Yen. In 2020, Viet Nam completed the pilot iDES in Phu Yen. The pilot was expanded to two additional provinces, Gia Lai and Binh Phuoc, in 2021. The NIMPE enrolled 13 P. falciparum cases for DHA-PPQ and 17 P. vivax cases for CQ iDES. Both indicated 100% efficacy, but the loss to follow-up was very high due to COVID-19 restrictions.

The majority of molecular markers of antimalarial drug resistance (P. falciparum chloroquine transporter gene, K13 (C580Y) & Plasmeisin-II copy number variations) are present in the provinces bordering Cambodia. The molecular markers indicate there is no mefloquine (MQ) resistance, except in Ninh Thuan province.
The current challenges for completing iDES are linked to limited government funding for malaria control and resistance research. In addition, many \textit{P. vivax} foci are emerging in the central and northern regions. Research activities are planned to manage the growing \textit{P. vivax} foci.

Despite these challenges, Viet Nam is currently implementing a range of operational research projects. A G6PD deficiency survey is ongoing in malaria-endemic areas. A separate study is being conducted on tracing genetic markers associated with resistance in both \textit{P. falciparum} and \textit{P. vivax} species. The Institute of Malariology Parasitology and Entomology Quy Nhon (IMPE) is supporting a large-scale survey of asymptomatic carriers in all malaria-endemic zones. Lastly, the NIMPE is working with the Australia Malaria Institute to conduct an \textit{in vitro} malaria parasite culture and molecular research study. Training courses for malaria experts and researchers are planned from 2022 to 2025 on malaria molecular markers, malaria parasite culture, and \textit{in vitro} tests.

Viet Nam continues to use the results of TES and iDES to support policy changes. Following evidence of the reduced sensitivity of DHA-PPQ, the national antimalarial drug policy changed from DHA-PPQ to AS-PY in 2020 for six provinces.

In 2022, Viet Nam plans to extend surveys of K13 monitoring. Clinical trials for tafenoquine (TQ) will be conducted for \textit{P. vivax}. Research is also planned on PQ adherence in the treatment of \textit{P. vivax} cases and the detection of \textit{P. vivax} hypnozoites.

In terms of QC, approvals are sought from the WHO ERC and NIMPE/IMPE independent review boards before conducting TES or iDES in field sites. QA and QC monitoring is conducted by the principal investigator or independent clinical monitors. External QA microscopy and polymerase chain reaction (PCR) validation is provided by WHO and the US Naval Medical Research Unit-2. Interim TES and iDES evaluations validate the malaria data. NIMPE and IMPE register all TES and iDES in the Australian New Zealand clinical trials registry.

2.5.5 Thailand

Ms Thannikar Tongard, Public Health Technical officer from Thailand’s DVBD, presented the iDES findings for Thailand. As Thailand’s case numbers continue to decline, the DVBD has replaced TES in favour of iDES. Overall, adherence to the NTGs continues to improve. In 2021, the NTGs for medical doctors and NTGs for public health officers were updated.

Follow-up rates among malaria patients continued to improve in 2021, resulting in more patients presenting for at least one follow-up visit compared to 2020. Follow-up rates are similar among both Thai and migrant populations as well as males versus females. These increasing follow-up rates help ensure successful treatment outcomes for patients.

iDES from 2020 indicate that the efficacy for DHA-PPQ in \textit{P. falciparum} cases was 98% in 2020 and 94.3% in 2021. CQ + PQ in \textit{P. vivax} cases showed efficacy rates of 97.1% in 2020 and 97.6% in 2021. Sisaket recorded efficacy rates lower than the national average in 2020 and 2021, respectively, with 70% and 85.7%.

Dr Rungniran Sugaram, DVBD Public Health Technical Officer, provided an overview of Thailand’s malaria cases. Recent iDES malaria species analysis has shown a few discordant species in microscopy versus PCR diagnosis, although overall microscopy readings are good. The results for molecular marker data collected from iDES in 2020 indicate that for K13 samples, nine cases were R561H and two were wild type.

A major challenge for iDES has been improving drug adherence and completion of follow-up. Other challenges include improving the quality of blood sample collection, maintaining regular supervision and monitoring in the field, and providing relevant training to maintain skills in low-burden settings.
Thailand’s ongoing research projects include clinical trials on the feasibility of TQ. In terms of mass drug administration, Thailand is completing studies on the use of AS-MQ among high-risk populations and the feasibility of G6PD biosensor testing. iDES, the Genome Project, Mahidol-Oxford Tropical Medicine Research Unit (MORU) and the Armed Forces Research Institute of Medical Sciences (AFRIMS) support molecular marker surveillance on K13 and other markers.

In the concluding remarks, Dr Rungniran noted that the treatment of *P. falciparum* and *P. vivax* malaria continues to be effective. The programme has found iDES to be a timely and useful tool for monitoring drug efficacy and improving NTGs. The DVBD will continue to improve drug adherence and follow-up for *P. vivax* cases receiving radical cure treatment.

Following the presentation, Dr Ringwald questioned the data for *P. vivax* in Sisaket. Dr Rungniran clarified that reported failure rates were for 90 days and that the efficacy at 28 days was very high. Sisaket recorded only 14 malaria cases this year. Dr Rungniran noted that reports of side-effects among patients taking AS-MQ were limited. For patients receiving AS-MQ, Thailand conducts supervised treatments on day 3 and day 4.

Dr Ringwald highlighted the significant number of *P. knowlesi* cases that were retrospectively diagnosed through PCR. He suggested a specific review of the clinical management and treatment response of these cases.

2.6 **Opening session of day 2**

Dr Tuseo opened the second day of the meeting and nominated Dr Keobouphaphone Chindavongsa, Deputy Director from the CMPE, Lao People's Democratic Republic, as chairperson for day 2.

2.7 **Quality control in therapeutic efficacy studies and integrated drug efficacy surveillance: implementation challenges**

Dr Maria Dorina Bustos provided an overview of QC in TES and iDES. Monitoring drug efficacy is a global public good and WHO's responsibility. Available data are stored in the WHO Global Database on Therapeutic Efficacy of Antimalarials and accessible through the Malaria Threats Maps. She noted that deviations in TES protocol sometimes occur during protocol development. Common issues relate to the lack of correct background information such as study dates, exact location, drug name, manufacturer and expiration date in adherence to *TES template 2018 v1.5.4*.

Protocol requirements to consider for microscopy include the fact that the inclusion of mixed infections can affect efficacy rates and can complicate slide reading and data analysis. Parasites should be expressed as the number of asexual parasites/μL of blood. Analysis should be made using an assumed white blood cell density of 6000/μL for TES. This is not to be confounded with the WHO-recommended white blood cell count of 8000/μL. WHO protocol considers a blood slide to be negative when no asexual parasites are seen after examining microscopic fields that include 1000 white blood cell counts. Protocol variations in these examinations and counting methods make certain comparisons difficult. Patients should be followed up, and slides must be examined beyond day 3 until a case is negative. Timely QC of slide readings remains the main challenge in many of the TES. Dr Bustos encouraged NMPs to take the average of M1 and M2 cell counts. If there is discordance between M1 and M2 readings/parasite counts, they must be validated by the M3 reading/count.

TES requires supervised treatment for all doses given, yet some studies do not supervise the second AL dose. In terms of classification of treatment outcomes, one major issue involves patients classified as early treatment failures on day 1 due to the development of severe malaria within the first 24 hours. This is rarely due to resistance but rather due to the inclusion criteria being disregarded (in such cases,
these patients should be excluded from the TES analysis). Early treatment failure is not synonymous with partial artemisinin resistance (delayed clearance) and vice versa. The analysis of the data allows the use per protocol and Kaplan-Meier methodologies. If parasite reappearance is identified during follow-up, confirmation should be completed by PCR analysis.

PCR analysis used in classifying *P. falciparum* patients as having recrudescence or reinfection sometimes differs from the methodology recommended in the WHO protocol. PCR correction is needed to prevent this, using merozoite surface protein (msp)1, msp2 and glutamate-rich protein (glurp). Sometimes, microsatellites or barcodes are used rather than msp1, msp2 and glurp. Thus, it is critical to clearly describe the molecular methods and algorithms used for these analyses to interpret comparability among studies. It is not recommended to merge data, except in very low transmission areas. Even in cases of low numbers of enrolled patients, data from all sites should be described separately because merged data from sites could obscure the appearance of emerging resistance.

WHO has developed QC monitoring templates, including checklists before, during and at the end of the study. QC reports by external clinical monitors are used in all countries implementing TES. They provide immediate documented feedback on gaps and challenges for improvement and allow monitors to follow up on recommendations. Dr Bustos provided an overview of the pre-study and interim visit QC checklist elements, including general study information, study sites and site-specific information, study-specific information and conclusions.

During the preparation phase of TES, common challenges include selecting study sites as annual trends change the available locations. Another issue relates to delays in protocol review and approvals by national stakeholders and the WHO ERC. Administrative delays and late reports can also impact the release of funds. Lastly, trials must be officially registered in the clinical trial registry before the study starts.

Common issues during QC monitoring include inconsistencies in the case report forms, such as transcription errors from the source document, missing data, crossed-out corrections and failure to record the second-line treatment in the case of treatment failure. Challenges with treatment include the lack of second-line drugs for rescue treatment in some district hospitals and health centres, no drug inventory or suboptimal drug storage conditions. Additional issues can arise in supervising treatments if a patient is not hospitalized. In the case of *P. vivax* cases, there can also be challenges in TES compliance for PQ administration for 14 days after ACT treatment.

During TES implementation, challenges include securing consent and developing protocols for pregnancy tests for females and minors (9–17 years) of child-bearing potential, as this may not be appropriate according to local cultures/customs. Consequently, female minors and unmarried women are excluded from efficacy studies in the GMS. Follow-up (after 28/42 days) can also be confounded in remote areas or during the rainy season. This may lead to missed follow-up days for monitoring.

Common issues observed in the laboratory phase relate to the quality of the microscopic blood examination. If the microscopy logbook of M1 and M2 is not available on-site, this can mean late or irregular validation by M3. Regular training is needed for staff to properly collect, label and store dried blood spots. In terms of the genotyping malaria parasites, issues arise when the genotyping of msp1, msp2 and glurp are done together and not sequentially. This confounds differentiating recrudescence from reinfection.

Another common problem is conducting timely assays as part of QC and identifying molecular markers for antimalarial drug resistance. For QA/QC, 10% of molecular procedures are sent to the WHO-appointed reference lab. It is compulsory to sign a material transfer agreement between countries and the reference laboratory for these transfers.

During data entry, common challenges in utilizing Excel forms include completing the study site and drug information, failing to enter information for cases that are lost to follow-up or withdrawn, or double data entry or validation from entry 1 to entry 2. A final issue is failing to enter PCR results once they become available from the reference laboratory.
In iDES, the effective implementation of malaria surveillance systems is crucial. Proper training is needed to ensure adherence to SOPs. Standardized reporting forms should be linked to laboratory forms. In terms of laboratory QC, microscopists at district hospitals and health centres often miss day zero slide and collection in the database or recording the day of failure. To avoid these issues, refresher training is needed for peripheral-level microscopists. Adherence to NTGs and drug availability at district and private hospitals require young doctors and staff to reorient to updated NTGs. NMPs should keep an inventory of the stock levels for both first- and second-line ACTs and intravenous artesunate or quinine/tetracycline for severe malaria cases.

iDES also requires resources for follow-up with hard-to-reach or mobile populations. Timely data entry is needed at field sites and district hospitals. Issues arise when there are delayed referrals or information from hospitals to malaria staff despite 24-hour case notification. A focal person should be available at the central level to regularly review data management and analysis. Another problem is that many patients do not complete the follow-up plan. There is a need to logistically plan for follow-up in the event of treatment failure. Not all hospital-treated cases follow the NTGs, and for non-hospitalized cases, it is important to ensure compliance with the treatment regime.

Consolidating surveillance reports and lab results can also prove challenging in iDES. In the Lao People's Democratic Republic, this challenge is mitigated by reporting malaria microscopy and RDT results in district hospitals using District Health Information System (DHIS) tracking forms. In Thailand, standardized reporting forms are now linked to laboratory forms.

### 2.8 Plenary discussion: question and answer session

During the discussion, Dr Bustos noted that given COVID-19 restrictions, monitoring exercises in the GMS are currently conducted by WHO country office staff who have been assigned to manage the on-site monitoring. If questions arise, locally based staff in the GMS countries liaise with WHO’s regionally based QC experts. Some countries have observed temporary suspensions in TES enrollment because of COVID-19 restrictions, with malaria medical staff reassigned to COVID-19 response teams.

Dr Ringwald reiterated that supervised treatment is required for TES and iDES. In iDES, countries are adapting to local conditions to find ways of assuring that the treatment is taken. The first dose of treatment under iDES is always supervised by health staff; documentation for patients taking subsequent doses are sometimes inadequate. The supervision protocol for the subsequent doses needs to be clearly recorded either as supervised, same-day visit or unsupervised dose. If iDES shows high numbers of treatment failures, confirmatory studies should be done, and a change in first-line treatment should be considered.

Dr Ringwald clarified that health staff should collect dry blood spots on day zero and day of failure to facilitate PCR correction. It is also recommended to take a filter paper at day zero and day of failure to track molecular markers.

Dr Ringwald noted that AS-MQ monitoring is straightforward due to the presence of a molecular marker. AS-PY does not have a molecular marker, which complicates monitoring. TES should be continued for AS-PY in countries such as the Lao People’s Democratic Republic. He stressed that bottlenecks in the non-availability of drugs across the GMS need to be managed effectively.

He also highlighted that a high positivity rate on day 3 does not contradict the results of ACPR. The positivity rate tracks artemisinin resistance, whereas the ACPR result relates to the efficacy of the partner drug.
2.9 Drug efficacy monitoring (of imported cases) in a malaria-free country

2.9.1 China

Dr Fang Huang, Researcher at China’s National Institute of Parasitic Diseases (NIPD), provided an overview of drug efficacy monitoring in China. China has not reported an indigenous case since 2016 and was subsequently declared malaria-free in 2021.

The current first-line treatment policy for *P. falciparum* malaria suggests three different types of ACTs. DHA-PPQ is most widely used, and artesunate-amodiaquine (AS-AQ) or artesunate-piperaquine (AS-PPQ) are also available. The first-line policy for *P. vivax* and *P. ovale* is CQ + PQ (eight days). PPQ, PY or ACTs are provided in the event of treatment failure. *P. malariae* cases receive CQ, PPQ, PY or ACTs are administered as second-line drugs. Severe malaria cases receive AS, artemether or a PY injection followed by an ACT.

Yunnan province has conducted iDES for *P. vivax* cases receiving CQ since 2020. All imported cases are screened and included in iDES. An updated iDES protocol according to WHO guidelines will be released in 2021 and will be rolled out in 2022. China also set up an antimalarial resistance monitoring system in 2016, which collects samples from imported cases.

In China’s prevention of reestablishment setting, challenges include the delivery of refresher training on microscopy and quality assurance. Loss to follow-up has been a challenge outside of Yunnan, as iDES protocols are new and not rolled out nationally. In the future, iDES will be integrated into the national surveillance system so that other local health centres can complete the follow-up. The protocol will likely be translated into English by 2022.

2.9.2 Sri Lanka

Dr Kumudu Gunasekera, Parasitologist from Sri Lanka’s Anti Malaria Campaign, delivered an overview of Sri Lanka’s experience in monitoring drug efficacy in a “prevention of reestablishment” setting. Sri Lanka was certified as malaria-free in 2016. Since then, it has continued monitoring the efficacy of drugs to avoid any treatment failures emerging among imported cases that may carry resistant malaria strains. Once a case is detected, the Anti Malaria Campaign completes a vigorous scope of work that includes treatment, record keeping, case investigation, response and follow-up procedures. Medical institutions work with regional and central offices of the Anti Malaria Campaign to complete microscopy analysis, perform RDTs (if needed) and collect blood for further assays.

Dr Gunasekera emphasized that iDES is a feasible routine activity in a prevention of reestablishment setting. In Sri Lanka, tailored instructions and guidelines have ensured that the studies continued throughout the COVID-19 pandemic. iDES provides valuable information on the treatment outcomes of imported malaria cases and ensures radical cure completion. The quality of iDES can be maintained through continuous training of relevant health staff. This is particularly important in relation to microscopy. Studies on genotyping and molecular markers of imported cases increased the level of certainty and understanding in epidemiological and clinical interpretations. They also served to improve the competence and capacity of the laboratories.

2.10 The threat of pfHRP2/3 deletions

Dr Jane Cunningham, Medical Officer from WHO’s Global Malaria Programme, delivered a presentation on the threat of *P. falciparum* histidine-rich protein 2 (pfHRP2) deletions. Histidine-rich protein 2 (HRP2) is a protein expressed only by *P. falciparum* and is the target for the most used RDTs. HRP2 RDTs generally have the highest sensitivity of the RDTs for *P. falciparum* malaria. HRP2 is found in the cytoplasm and surface of *P. falciparum*-infected erythrocytes. HRP3 is closely linked to
HRP2, and RDTs that target HPR2 can, to some extent, detect HRP3. Peru recorded the first deletion of pfHRP2 in 2010, and this led to the NMP pivoting away from RDTs in favour of microscopy. The deletion has since been detected in countries across Africa and Asia.

In 2017, WHO published an information note on false-negative RDT results in P. falciparum patients. HRP2 deletions should be suspected in a patient that gives negative results on a pfHRP2 test line in at least two quality-assured malaria RDTs and a positive on the pan- or P. falciparum parasite lactate dehydrogenase (pLDH) test line, when a combination test is used, and the sample is confirmed microscopically to be positive for P. falciparum by two qualified microscopists.

PfHRP2/3 deletions can be indicated at a programmatic level if there are rates of discordance ≥ 10–15% between RDTs and microscopy. NMPs should keep note of anecdotal evidence or formal complaints regarding false negatives of RDTs. When pfHRP2/3 deletions are reported, the baseline prevalence should be determined in the affected and neighbouring countries.

WHO has subsequently developed protocol templates on the surveillance of suspected malaria cases and another on surveillance and biobanking to identify pfHRP2/3 deletions. If a survey confirms the presence of HRP2/3 deletions is causing false-negative pfHRP2-RDTs greater than 10–15%, then the NMP will need to take a series of actions to optimize case management immediately and plan for the introduction of replacement RDTs. Any change should be applied nationwide, although NMPs might prioritize rollout on the basis of the prevalence of pfHRP2/3 deletions.

WHO tracks global HRP2/3 deletions through the Malaria Threat Maps. Data from the GMS are limited to two studies from the China-Myanmar border from 2004 samples where the presence of HRP2/3 deletions was confirmed. However, we do not know the impact on pfHRP2-sensitive RDTs, and there is a need for further studies in Myanmar and surrounding countries. Globally, many countries want to conduct pfHRP2/3 surveys but lack funding. The U.S. President’s Malaria Initiative (PMI) and the Bill and Melinda Gates Foundation have expressed interest in supporting surveillance of pfHRP2/3 through TES and molecular surveillance projects.

Dr Cunningham issued some cautionary notes about TES for pfHRP2/3 surveillance. There are many differences between the TES and WHO template for pfHRP2/3 surveillance. If a TES identifies pfHRP2/3 deletions, they support the need for a larger and broader survey. Still, if no pfHRP2/3 deletions are found, it doesn’t allow NMPs to conclude that pfHRP2/3 deletions are not present at potentially clinically relevant thresholds.

Eritrea’s experience indicates that pfHRP2/3 deletions can persist despite removing the pressure of pfHRP2 RDTs. Both Eritrea and Djibouti have changed RDTs, and there are plans to change the RDTs in the Tigray and Amhara regions of Ethiopia.

In her concluding remarks, Dr Cunningham emphasized that surveillance should be a high priority for all countries, particularly where pfHRP2/3 deletion have been reported locally or regionally. With continued pfHRP2 RDT pressures, we should expect that the problem is ongoing and commit to surveying for the deletions.

2.11 Moving forward on the effective management and monitoring of P. vivax malaria in the Greater Mekong Subregion

Dr Tuseo delivered an overview of the P. vivax treatment regime in each of the GMS countries. The efficacy of drugs for treating P. vivax ranges from 94.7% to 100% in the GMS countries. G6PD tests are provided to P. vivax patients in Cambodia and the Lao People’s Democratic Republic. Although G6PD testing is included in the NTGs of Thailand and China, they are not routinely used. G6PD tests are only provided in Viet Nam if required. In Myanmar, the current policy is treatment without testing. However, in states with high G6PD deficiency prevalence (such as 18–20% in Kayin state), the NMCP guides partners in testing and treatment. For patients receiving PQ, per NTG, supervised treatment is provided in Cambodia, China (through iDES monitoring), the Lao People’s Democratic Republic,
Myanmar and Viet Nam (when funding is available). Although supervised PQ treatment is included in Thailand’s NTG, it is provided through iDES monitoring in practice.

Ms Charlotte Rasmussen, Technical Officer from WHO’s Global Malaria Programme, provided an overview of TES and iDES in *P. vivax* cases. TES for *P. vivax* infections look at the efficacy and resistance to treating the asexual blood-stage parasites. Concomitant treatment against liver-stage parasites can increase the efficacy of treatment against resistant blood-stage parasites. Therefore, radical treatment against the liver-stage parasites is moved to day 28 if locally acceptable.

A recurrent blood-stage infection following treatment of *P. vivax* can be a relapse (due to activation of hypnozoite), a recrudescence (due to blood-stage treatment failure) or reinfection. Therefore, one of the challenges with TES for *P. vivax* malaria is distinguishing recrudescence, infection and relapse. Sufficient drug blood concentration should prevent both recrudescence and relapse. If the drug given to a patient has a long half-life (and has been absorbed as expected), recurrent parasitemia would not be expected before day 28.

*P. vivax* CQ treatment failure on or before day 28 has been observed in a number of countries, including those in the GMS. *P. vivax* CQ resistance may be confirmed using blood samples collected on day 7, the day of failure, or on day 28.

To prevent relapses, *P. vivax* patients need to be treated with PQ, an 8-aminoquinoline. Studies of the efficacy of PQ in preventing relapse can be combined with routine TES that examine the efficacy of the blood schizonticide. The period of follow-up should be adapted to the regional relapse characteristics of the parasite. The follow-up phase varies in the literature from three to 12 months. The ideal follow-up period for all areas is 12 months.

PQ is a prodrug that requires in vivo conversion into active metabolites to have an effect against hypnozoites. Studies have shown that cytochrome P450 2D6 (CYP2D6) is critical in the metabolic activation of PQ. Hence, where PQ adherence is confirmed, CYP2D6 polymorphisms represent the most probable cause of PQ treatment failures and need to be investigated. PQ failure is defined as a confirmed positive blood smear for *P. vivax* during the follow-up phase after treatment with an effective blood schizonticide and PQ therapy, in a patient whose reinfection has been prevented. Ideally, PQ efficacy should be studied in an environment where there is no risk of reinfection. In settings where there is a risk of reinfection, it is impossible to make conclusions regarding the cause of recurrent *P. vivax* infection in individual patients. Nevertheless, data collected from many patients may offer insights about the efficacy of PQ when compared with the general relapse rate in an area or in a control group that does not receive PQ.

iDES happens in the context of a malaria elimination programme where activities aim to ensure that all patients are cured, and malaria parasites are not transmitted. For *P. vivax* patients, this means ensuring that both the asexual blood-stage parasites and liver-stage parasites are eliminated (and thus relapses prevented).

In the concluding remarks, Ms Rasmussen highlighted that further information could be accessed through the WHO Malaria Threat Maps and the recently published *Report on Antimalarial Drug Efficacy, Resistance and Response*.

### 2.12 Partner inputs

Dr David Sintasath, Regional Malaria Advisor at PMI, welcomed the more concrete discussions on iDES presented during the meeting. He encouraged countries to utilize the additional financial resources made available to countries because of COVID-19. Many of these funds are active until 2023 and link to the GMS timeline to eliminate *P. falciparum* malaria. Governments should take advantage of these resources to implement some of the supervised treatments under iDES.
Mr Matteo Dembech, Technical Officer from the Regional Artemisinin-resistance Initiative (RAI) Regional Steering Committee (RSC), provided an update on behalf of the Independent Monitoring Panel (IMP). The IMP recently commissioned malaria experts to review 8-aminoquinoline therapy for *P. vivax* malaria in the GMS. The resulting document will be shared with the RAI RSC very soon. The review is expected to contribute to ongoing deliberations concerning the best ways forward with the radical cure for *P. vivax* malaria in the GMS. In addition, IMP and the MME programme have teamed up to produce a series of “programme trajectory” maps for the GMS showing the change in the number of *P. falciparum* cases in the last 12 months relative to the previous 12 months, month by month from 2010. The plan is to annotate these maps with the help of key informants and animate the time series to produce a video that should provide a clearer understanding of the intensity, geographical scale and duration of the impact of various factors on the trajectory of malaria elimination efforts in the GMS in recent years.

3. CONCLUSIONS AND RECOMMENDATIONS

Dr Tuseo concluded the meeting by summarizing the presentations and thanking the GMS country participants, the donors and partners for their comments and support, and the WHO Secretariat.

3.1 Conclusions

**Overview of GMS malaria elimination:** From January to July 2021, the GMS countries recorded a 26% reduction in malaria cases when compared to the same period in 2020. At the same time, *P. falciparum* + mixed cases fell by 55%, while *P. vivax* cases dropped by 19%.

**Drug efficacy:** In 2021, quality TES and monitoring were completed in four GMS countries: Cambodia, the Lao People’s Democratic Republic, Myanmar and Viet Nam. As malaria case numbers continue to drop, iDES continues to be implemented nationwide in Thailand and to be rolled out in Viet Nam and the Lao People’s Democratic Republic. Cambodia started an iDES pilot in three districts in one province. While artesunate-pyronaridine (AS-PY) is registered as an alternative ACT and a second-line drug, use is limited in Cambodia and the Lao People’s Democratic Republic due to supply issues.

- **Cambodia:** Artesunate-mefloquine (AS-MQ) and AS-PY continue to demonstrate efficacy for *P. falciparum* and *P. vivax* malaria. In 2020, TES indicated that the efficacy of AS-MQ remains high.

- **Lao People’s Democratic Republic:** AS-MQ and AS-PY remain efficacious. The data on artemether-lumefantrine (AL) from 2019-2020 show high efficacy compared to 2018 against *P. falciparum* and *P. vivax* malaria with a larger sample size than was achieved in 2018. Molecular data indicated fewer K13 mutations compared to 2018 except in Champassak province, mefloquine sensitivity was present in all samples assayed and Plasmepsin2 copy number decreased, showing a reversal of piperaquine resistance.

- **Myanmar:** AL, AS-PY and dihydroartemisinin-piperaquine (DHA-PPQ) remain efficacious. Similarly, chloroquine (CQ) for *P. vivax* cases also remains efficacious.

- **Viet Nam:** AS-PY and AS-MQ are efficacious. In September 2020, treatment failures with DHA-PPQ led to two additional provinces (Phu Yen and Khanh Hoa) switching to AS-PY. Molecular data indicate piperaquine (PPQ) resistance along the provinces bordering Cambodia.

- **Thailand:** DHA-PPQ for *P. falciparum* cases is efficacious where data is available, except in Sisaket province, bordering Cambodia, where AS-PY is the first-line treatment. CQ + primaquine (PQ) for *P. vivax* cases also remains efficacious.
**Quality control in TES and iDES:** Adherence to WHO’s quality assurance (QA) and quality control (QC) protocols are mandatory. Common deviations should be noted to avoid incorrect or missing information. QA and QC were maintained through regular monitoring and communication between WHO country staff, NMP investigators and the WHO regional drug resistance monitor despite pandemic restrictions.

**Efficacy monitoring in a malaria-free setting:** iDES is feasible as a routine activity in a “prevention of reestablishment” setting. The continuous training of relevant health staff, particularly in microscopy, is essential to ensure the effectiveness of iDES among imported cases.

**pfHRP2/3 deletions:** Histidine-rich protein 2 (HRP2) is a protein expressed only by *P. falciparum* and is the target for the most used RDTs. HRP2 RDTs generally have the highest sensitivity of the RDTs for *P. falciparum* malaria. However, parasite strains in several countries have been identified that have deletions in the genes encoding HRP2 or the similar HRP3 protein. Studies done in the past on the Myanmar-China border detected the presence of parasites with pfHRP2/3 deletions. Surveys and studies are needed to map the prevalence and impact of pfHRP2/3 deletions in the subregion. NMPs should keep note of anecdotal evidence or formal complaints regarding false-negative RDTs, as this may indicate the presence of pfHRP2/3 deletions.

**Effective management and monitoring of *P. vivax* malaria:** The efficacy of drugs for treating *P. vivax* in the GMS ranges from 94.7% to 100%. But there are challenges in the 14-day PQ radical treatment and monitoring for relapse or reinfection beyond day 28/42 in iDES. Routine TES for *P. vivax* infections look at efficacy and resistance to the treatment of the asexual blood-stages parasites.

**Supervised treatments:** Supervised treatment is required for TES and iDES. In iDES, countries are adapting to local conditions to find ways of assuring that the treatment is taken. The first dose of treatment under iDES is always supervised by health staff; documentation for patients taking subsequent doses are sometimes inadequate. If iDES shows high numbers of treatment failures, confirmatory studies should be done, and a change in first-line treatment should be considered.

### 3.2 Recommendations

#### 3.2.1 Recommendations for Member States

Member States were encouraged to consider the following:

1) Continue monitoring the quality of TES implementation based on the WHO QC checklist while ensuring the safety of front-line workers in the context of the COVID-19 pandemic.

2) Continue to review the results of TES within countries and consider switching the first-line drug nationally rather than subnationally.

3) Continue to refine and roll out iDES, where feasible, as countries approach elimination and the number of malaria cases decreases. Ensure integration of iDES with laboratory microscopy and procedures to measure molecular markers. Cambodia is encouraged to pilot iDES through existing mechanisms with simple SOPs, training and supervision of health staff and village malaria workers to further strengthen the national surveillance system.

4) In the context of COVID-19, test suspected cases as per national guidelines, ensuring compliance to infection prevention and control measures and safety of the patients and the health staff.

5) Continue efforts to strengthen QA for microscopy, especially at the peripheral level for achieving elimination.
6) Continue to strengthen microscopy capacity during the COVID-19 pandemic using innovative methods, such as the virtual External Competency Assessment of Malaria Microscopists (ECAMM), where feasible.
7) Continue efforts to strengthen QA in molecular assays and analyse trends in the GMS.
8) The reversal of mefloquine resistance in Cambodia and the return of efficacy of AS-MQ have highlighted the potential for reintroducing failed drugs. However, maintaining strong surveillance of AS-MQ efficacy in Cambodia remains a priority.
9) The situation should be closely monitored in Viet Nam after the full implementation of AS-PY with regards to KEL1/PLA1, as the country still uses DHA-PPQ in other provinces.
10) As CQ resistance in *P. vivax* parasites has been identified in the past in the GMS, continue monitoring through iDES. Results for CQ efficacy studies should be reported at day 28 and day 90 follow-up.

3.2.2 Recommendations for WHO

1) The WHO Regional Office is requested to support countries to review and revise NTGs based on available TES and iDES data and coordinate bottleneck resolutions with NRAs.
2) The Global Malaria Programme and MME programme is requested to provide support to GMS countries on TES protocol development and implementation based on standard guidelines, national workplans and budgets:
   a) Support countries moving towards elimination, particularly as they transition to iDES, including finalizing the iDES protocol and scaling up activities to ensure drug efficacy in elimination settings; and
   b) Coordinate with partners on potential pooled drug procurements, especially second-line artemisinin-based combination therapies (ACTs) (in low quantities).
3) The country offices are requested to support the operationalization of revised national treatment guidelines and the expansion, strengthening and monitoring of iDES.
## Programme agenda

<table>
<thead>
<tr>
<th>Date and Time</th>
<th>Agenda</th>
<th>Speaker</th>
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<tbody>
<tr>
<td><strong>Wednesday 15 September 2021</strong></td>
<td><strong>Chairperson for Day 1: Prof. Tran Thanh Duong, Director, NIMPE, Viet Nam</strong></td>
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<tr>
<td>Opening Ceremony</td>
<td>Welcome address from WHO Representative Cambodia</td>
<td>Dr Li Ailan (WHO)</td>
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<td>Opening remarks from WHO Global Malaria Programme</td>
<td>Dr Pascal Ringwald (WHO)</td>
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<td></td>
<td>Meeting objectives and introduction of the meeting chairs for both days</td>
<td>Dr Luciano Tuseo (WHO)</td>
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<td></td>
<td>Administrative - virtual meeting rules and announcements</td>
<td>Dr Maria Dorina Bustos (WHO)</td>
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<tr>
<td><strong>Session 1: Regional updates</strong></td>
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<tr>
<td>13:30 – 13:45</td>
<td>Review of recommendations from 2020 and progress</td>
<td>Dr Maria Dorina Bustos (WHO)</td>
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<tr>
<td>13:45 – 14:15</td>
<td>Updates from the Mekong Malaria Elimination programme in the GMS</td>
<td>Dr Luciano Tuseo (WHO)</td>
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<td></td>
<td>(to include issues such as COVID and other MME updates)</td>
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<tr>
<td>14:15 – 14:30</td>
<td>Plenary Discussion</td>
<td>All participants</td>
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<td>14:30 – 14:40</td>
<td>Coffee/tea break (on your own)</td>
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<tr>
<td><strong>Session 2: Country Presentations: Results and future priorities / plans / studies needed</strong></td>
<td>(30 mins country presentation and 15 mins discussion per country)</td>
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<tr>
<td>14:40 – 15:25</td>
<td>Cambodia</td>
<td>CNM TES Principal Investigator</td>
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<td>15:25 – 16:10</td>
<td>Lao People's Democratic Republic</td>
<td>CMPE TES Principal Investigator</td>
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<td>16:10 – 16:55</td>
<td>Myanmar</td>
<td>DMR TES principal Investigator</td>
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<td>16:55 – 17:40</td>
<td>Viet Nam</td>
<td>NIMPE Principal Investigator</td>
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<td><strong>Day end</strong></td>
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<tr>
<td><strong>Thursday 16 September 2021</strong></td>
<td><strong>Chairperson for Day 2: Dr Keobouphaphone Chindavongsa, Deputy Director, CMPE, Lao People’s Democratic Republic</strong></td>
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<td>Session 2: Continuation from day 1 country presentations</td>
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<tr>
<td>13:00 – 13:45</td>
<td>Thailand</td>
<td>DVBD Principal Investigator</td>
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<td>13:45 – 14:25</td>
<td>Quality Control in TES and iDES: implementation challenges (MM QA, classification, monitoring, etc.)</td>
<td>Dr Maria Dorina Bustos (WHO)</td>
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<tr>
<td>14:25 – 15:00</td>
<td>Plenary discussion Q&amp;A</td>
<td>All</td>
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<td>15:00 – 15:10</td>
<td>Coffee/tea break (on your own)</td>
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<td><strong>Session 3: Specific technical presentations</strong></td>
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<td>15:10 – 15:50</td>
<td>Drug efficacy monitoring (of imported cases) in a malaria-free country – China and Sri Lanka</td>
<td>China – Dr Fang Huang, National Institute of Parasitic Diseases Sri Lanka – Dr Kumudu Gunasekera, Anti Malaria Campaign</td>
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<td>15:50 – 16:20</td>
<td>HRP2 deletions</td>
<td>Dr Jane Cunningham (WHO)</td>
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<td>16:20 – 16:50</td>
<td>Moving forward on the effective management and monitoring of <em>P. vivax</em> malaria in the GMS</td>
<td>Dr Luciano Tuseo and Ms Charlotte Rasmussen (WHO)</td>
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<td><strong>Session 4: Partners</strong></td>
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<tr>
<td>16:50 – 17:05</td>
<td>Partner Inputs</td>
<td>All</td>
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<tr>
<td>17:05 – 17:10</td>
<td>Coffee/tea break (on your own)</td>
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<td><strong>Session 5: Closing remarks</strong></td>
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<tr>
<td>17:10 – 17:25</td>
<td>Closing remarks, conclusion, next steps and recommendations</td>
<td>Dr Luciano Tuseo (WHO)</td>
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<td><strong>Day end</strong></td>
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</tbody>
</table>
ANNEX 2

List of participants

GOVERNMENT PARTICIPANTS

Dr Chea Huch, Deputy Director, National Centre for Entomology and Parasitology Control, N° 372, Preah Monivong, corner Street 322, Phnom Penh, Cambodia, email: huch.cnm@gmail.com

Dr Leang Rithea, Vice Chief of Technical Bureau, National Centre for Parasitology Entomology & Malaria Control, N° 372, Preah Monivong, corner Street 322, Phnom Penh, Cambodia, email: rithealeang@gmail.com

Dr Siv Sovannaroth, Chief of Technical Bureau, National Centre for Entomology and Parasitology Control, N° 372, Preah Monivong, corner Street 322, Phnom Penh, Cambodia, email: sivosvannaroths@gmail.com

Dr Keobouphaphone Chindavongsa, Deputy Director, Centre for Malaria, Parasitology and Entomology, N° 365, Unit 22, DongDok village, Xaythany district, Vientiane, Lao People’s Democratic Republic, email: Chinda07@gmail.com

Dr Vonethalom Thongpraseurth, Vice Head, Malaria Diagnosis and Case Management Division, Centre for Malaria, Parasitology and Entomology, N° 365, Unit 22, DongDok village, Xaythany district, Vientiane, Lao People’s Democratic Republic, email: phoutnalongvilay@gmail.com

Dr Somphane Sengphinthong, Vice Head, Malaria Diagnosis and Case Management Division, Centre for Malaria, Parasitology and Entomology, N° 365, Unit 22, DongDok village, Xaythany district, Vientiane, Lao People’s Democratic Republic, email: t.vonethalom@gmail.com

Dr Maniphone Khanthavong, Technical Staff, Malaria Diagnosis and Case Management Division, Centre for Malaria, Parasitology and Entomology, N° 365, Unit 22, DongDok village, Xaythany district, Vientiane, Lao People’s Democratic Republic, email: kv.maniphone@gmail.com

Dr Khin Lin, Deputy Director General (Retired), National Malaria Control Program, Department of Public Health, Office No. 4, Nay Pyi Taw, Myanmar, email: dr.khinlin.dir@gmail.com

Dr Moe Kyaw Myint, Director, Department of Medical Research (Pyin Oo Lwin Branch), Office No. 4, Nay Pyi Taw, Myanmar, email: dr.myintmoekyaw@gmail.com

Mr Prayuth Sudathip, Public Health Technical Officer, Senior Professional Level, Division of Vector Borne Diseases, Department of Disease Control, Ministry of Public Health, 88/21 Taladkwan Sub-district, Muang District, Nonthaburi, Thailand, email: psudathip@gmail.com
Ms Aungkana Saejeng, Medical Technologist, Senior Professional Level, Division of Vector Borne Diseases, Department of Disease Control, Ministry of Public Health, 88/21 Taladkwan Sub-district, Muang District, Nonthaburi, Thailand, email: aung.saejeng@gmail.com

Ms Thannikar Tongard, Public Health Technical Officer, Senior Professional Level, Division of Vector Borne Diseases, Department of Disease Control, Ministry of Public Health, 88/21 Taladkwan Sub-district, Muang District, Nonthaburi, Thailand, email: tani_pui101@hotmail.com

Prof Tran Thanh Duong, Director, National Institute of Malariology, Parasitology and Entomology, #34, Trung Van Street, Nam Liem district, Hanoi, Viet Nam, email: tranthanhduong@hotmail.com

Dr Bui Quang Phuc, Head of Department of Clinical and Experimental Research, National Institute of Malariology, Parasitology and Entomology, 245 Luong The Vinh Street, Nam Tu Liem District, Hanoi, Viet Nam, email: phucnimpe@yahoo.com

Dr Huynh Hong Quang, Vice-Director, Head of Tropical Diseases Research and Treatment, Institute of Malariology, Parasitology and Entomology, Quy Nhon, 611B Nguyen Thai Hoc road, Quy Nhon city, Binh Dinh province, Quy Nhon, Viet Nam, email: huynhquangimpe@yahoo.com

Dr Doan Binh Minh, Vice-Director, Head of Entomology Department (IMPE Ho Chi Minh City), National Institute of Malariology, Parasitology and Entomology, 245 Luong The Vinh Street, Nam Tu Liem District, Hanoi, Viet Nam, email: doanbinhminhv@yahoo.com.vn

Ms Vo Bui Cao Thien, Doctor, Clinic, (IMPE Ho Chi Minh City), National Institute of Malariology, Parasitology and Entomology, #685, Tran Hung Dao Street, Ward 1, District 5, Ho Chi Minh, Viet Nam, email: caothiendhtn@gmail.com

Dr Fang Huang, Researcher of National Institute of Parasitic Diseases, Chinese Center for Disease Control and Prevention, 6 Xiyuan Road, Simao District, Puer, Yunnan, 665000, P.R. China, email: huangfang@nipd.chinacdc.cn

Dr Hui Liu, Director Technician of Yunnan Institute of Parasitic Diseases, 6 Xiyuan Road, Simao District, Puer, Yunnan, 665000, P.R. China, email: liubible@126.com

Dr Siqi Wang, Intern Researcher of National Institute of Parasitic Diseases, Chinese Center for Disease Control and Prevention, 6 Xiyuan Road, Simao District, Puer, Yunnan, 665000, P.R. China, email: wangsq@nipd.chinacdc.cn

TEMPORARY ADVISERS

Dr Iwagami Moritoshi, Parasitology Laboratory, Institut Pasteur du Laos, Samsenthai Road, Ban Kao-Gnot, Sisattanak District, P.O. Box 3560, Vientiane, Lao People’s Democratic Republic, email: iwagami@hotmail.com

OBSERVERS

Dr Jonathan Cox, Senior Program Officer, Malaria, Global Health Program, 440 5th Ave N., Seattle, WA 98109, Washington, Unites States of America, email: jonathan.cox@gatesfoundation.org

Dr Rida Slot, Project Management Specialist (Malaria), Office of Public Health and Education, USAID-Cambodia, American Embassy, #1, Street 96, Sangkat Wat Phnom, Khan Daun Penh Phnom Penh, Cambodia, email: rslot@usaid.gov
Dr Michael Thigpen, Captain, US Public Health Service, Resident Advisor, Office of Public Health and Education, USAID-Cambodia, American Embassy, #1, Street 96, Sangkat Wat Phnom, Khan Daun Penh, Phnom Penh, Cambodia, email: mthigpen@usaid.gov

Dr Lenna Neat Arango, Resident Advisor, Office of Public Health and Education, USAID-Cambodia American Embassy, #1, Street 96, Sangkat Wat Phnom, Khan Daun Penh, Phnom Penh, Cambodia, email: lneat@usaid.gov

Dr Saad El-Din Hassan, Resident Advisor, Office of Public Health and Education, USAID-Cambodia American Embassy, #1, Street 96, Sangkat Wat Phnom, Khan Daun Penh, Phnom Penh, Cambodia, email: shassan@usaid.gov

Dr Nu Nu Khin, Project Management Specialist (Health Program Manager), U.S. President's Malaria Initiative (PMI), Global Health Security, American Embassy, 110 University Avenue Road, Yangon, Myanmar, email: nnkhin@usaid.gov

Dr Mark Maire, CDC Resident Advisor, Division of Parasitic Diseases and Malaria, Center for Global Health, U.S. Centers for Disease Control and Prevention, American Embassy, 110 University Avenue Road, Yangon, Myanmar, email: mmaire@usaid.gov

Dr Gunawardena Dissanayake, USAID/PMI, U.S. President's Malaria Initiative (PMI), Global Health Security, Office of Public Health, USAID/ Burma, American Embassy, 110 University Avenue Road, Yangon, Myanmar, email: gdissanayake@usaid.gov

Mr David Sintasath, Resident Advisor for Malaria, Regional Development Mission for Asia (RDMA), Athenee Tower, 25th Floor, 63 Wireless Road, Bangkok, Thailand, email: dsintasath@usaid.gov

Ms Niparueradee Pinyajeerapat, Project Management Specialist (Public Health), Regional Development Mission for Asia (RDMA), Athenee Tower, 25th Floor, 63 Wireless Road, Bangkok, Thailand, email: npinyajeerapat@usaid.gov

Mr Izaskun Gaviria, Senior Fund Portfolio Manager, High Impact Asia Grant Management Division, The Global Fund to Fight AIDS, Tuberculosis and Malaria, Global Health Campus, Chemin du Pommier 40, 1218 Grand-Saconnex, Geneva, Switzerland, email: Izaskun.Gaviria@theglobalfund.org

Mr Soso Getsadze, Specialist, Health Products Management, High Impact Asia Department, Global Health Campus, The Global Fund to Fight AIDS, Tuberculosis and Malaria, Chemin du Pommier 40, 1218 Grand-Saconnex, Geneva, Switzerland, email: Soso.Getsadze@theglobalfund.org

Ms Rosie Ameyan, Senior Program Officer, The Global Fund to Fight AIDS, Tuberculosis and Malaria, Global Health Campus, Chemin du Pommier 40, 1218 Grand-Saconnex, Geneva, Switzerland, email: Rosie.Ameyan@theglobalfund.org


Ms Anna Sarkissian, Senior Program Officer, The Global Fund to Fight AIDS, Tuberculosis and Malaria, Global Health Campus, Chemin du Pommier 40, 1218 Grand-Saconnex, Geneva, Switzerland, email: Anna.Sarkissian@theglobalfund.org

Dr Jim Tulloch, Independent Monitoring Panel (IMP) Chair, RAI-Regional Steering Committee Secretariat, email: jimtulloch09@gmail.com
Dr Sean Hewitt, Independent Monitoring Panel (IMP) Member, RAI-Regional Steering Committee Secretariat, email: sean.hewitt@vbdc-consulting.com

Dr Faisal Mansoor, Head of the Programme Principal Recipient for The Global Fund, 12 (O)m Pyithu Lane, Township, Yangon, Myanmar, email: FaisalM@unops.org

Dr Eisa Hamid, Regional Senior Programme, M&E and Health Systems Specialist, 12 (O)m Pyithu Lane, Township, Yangon, Myanmar, email: eisah@unops.org

Dr Muhammad Farooq Sabawoon, Programme and M&E Specialist, Samdech Sothearas Blvd (3), Corner of Shihanouk (Street 274), Center 6th Floor Room 628 1230, Phnom Penh, Cambodia, email: farooqs@unops.org

Dr Yu Nandar Aung, Program and M&E Specialist, Office of the Resident Coordinator UN House, Lane Xang Avenue, PO Box 345, Vientiane, Lao People’s Democratic Republic, email: YunandarA@unops.org

Dr Zaw Win Tun, Public Health Officer, 12 (O)m Pyithu Lane, Township, Yangon, Myanmar, email: zawwint@unops.org

Dr Min Min Zin, Monitoring and Evaluation Officer (Malaria), 12 (O)m Pyithu Lane, Township, Yangon, Myanmar, email: MinZ@unops.org

Dr Myat Yi Lwin, Programme Management Specialist , 12 (O)m Pyithu Lane, Township, Yangon, Myanmar, email: myatyil@unops.org

Ms Cecilia Hugo, Executive Coordinator, ACT Malaria Foundation, Inc., 12th Floor Regus Centre, Times Plaza Bldg. corner UN and Taft Avenue, Ermita, Manila, Philippines, email: cecil_hugo@actmalaria.net

Mr Jacob Acker, Regional Malaria Manager, 7th Floor, No. 49 Kyun Taw Street, Sanchaung Township, Yangon, Myanmar, email: jacker@clintonhealthaccess.org

Ms Evelyn Wong, Regional Case Management Advisor, 7th Floor, No. 49 Kyun Taw Street, Sanchaung Township, Yangon, Myanmar, email: ewong@clintonhealthaccess.org

Dr Frank Smithuis, Associate Professor Oxford University, Director, Medical Action Myanmar (MAM), Myanmar Oxford Clinical Research Unit (MOCRU), Yangon, Myanmar, email: frank.m.smithuis@gmail.com

Prof. Arjen M. Dondorp, Deputy Director and Head, Global Fund Regional Artemisinin Resistance Initiative’s Regional Steering Committee, Bangkok, Thailand, email: arjen@tropmedres.ac

Mr Rikard Elfving, Social Development Specialist, Asian Development Bank, Phnom Penh, Cambodia, email: relfving@adb.org

Dr Megan Counahan, Health Adviser, Australian Embassy, No.16B National Assembly Street, Phnom Penh, Cambodia, email: Megan.Counahan@dfat.gov.au

Dr Ferdinal M. Fernando, Assistant Director and Head of the Health Division, Human Development Directorate, ASEAN Socio-Cultural Community Department ASEAN Secretariat, 70 A Jalan Sisingamangaraja, Jakarta, Indonesia, email: ferdinal.fernando@asean.org
Ms Amita Chebbi, Senior Director, Asia Pacific Malaria Elimination Network (APMEN), 11 Biopolis Way, #04-01/02 Helios, Singapore, Singapore, email: achebbi@aplma.org

SECRETARIAT

Dr Pascal Ringwald Coordinator, Drug Resistance and Containment, Global Malaria Programme, 20 Avenue Appia, Geneva, Switzerland, email: ringwaldp@who.int

Ms Charlotte Rasmussen, Technical Officer, Global Malaria Programme, 20 Avenue Appia, Geneva, Switzerland, email: rasmussenc@who.int

Dr James Kelley, Technical Officer, Regional Office for the Western Pacific, P.O. Box 2932, Manila, Philippines, email: kelleyj@who.int

Dr Neena Valecha, Regional Advisor, Malaria, Department of Communicable Diseases I.P. Estate, Mahatama Gandhi Marg, 110002, New Delhi, India, email: valechan@who.int

Dr Risintha Gayan Premaratne, Technical Officer, Department of Communicable Diseases I.P. Estate, Mahatama Gandhi Marg, 110002, New Delhi, India, email: premaratner@who.int

Dr Maria Dorina Bustos, Technical Officer, Malaria, 88/20 Permanent Secretary Building Ministry of Public Health Tiwanon Road 11000, Nonthaburi, Thailand, email: bustosm@who.int

Dr Deyer Gopinath, Medical Officer, Malaria, 88/20 Permanent Secretary Building Ministry of Public Health Tiwanon Road 11000, Nonthaburi, Thailand, email: gopinathd@who.int

Dr Badri Thapa, Scientist (Malaria Control), No. 403 (A1), Shwe Taung Kyar Street, Bahan Township Yangon, Myanmar, email: thapab@who.int

Dr Matthew Shortus, Medical Officer, 125 Saphanthong Road, Unit 5 Ban Saphanthongtai, Sisattanak District, Vientiane, Lao People’s Democratic Republic, email: shortusm@who.int

Dr Chitsavang Chanthavisouk, Technical Officer, 125 Saphanthong Road, Unit 5 Ban, Saphanthongtai, Sisattanak District, Vientiane, Lao People’s Democratic Republic, email: chanthavisoukc@who.int

Dr Ngon Sapal Mya, Medical Officer, Malaria, 63 Tran Hung Dao Street, Hoan Kiem District, Ha Noi, Viet Nam, email: ngonm@who.int

Dr Tran Cong Dai, Technical Officer, Malaria, 63 Tran Hung Dao Street, Hoan Kiem District, Ha Noi, Viet Nam, email: TranCongD@who.int

Dr Robert E. Kezaala, Medical Officer, 401, Dongwai Diplomatic Office Building, 23, Dongzhimenwai Dajie Chaoyang District, Beijing, PR China, Email: kezaalar@who.int

Dr Luciano Tuseo, MME Coordinator, No. 61-64, Preah Norodom Blvd. (corner St. 306) Sangkat Boeung Keng Kang I, Khan Chamkamorn, Phnom Penh, Cambodia, email: tuseol@who.int

Dr Zaixing Zhang, Medical Officer, No. 61-64, Preah Norodom Blvd. (corner St. 306), Sangkat Boeung Keng Kang I, Khan Chamkamorn, Phnom Penh, Cambodia, email: zhangz@who.int
Mr Rady Try, Technical Officer (Database Manager), No. 61-64, Preah Norodom Blvd. (corner St. 306), Sangkat Boeung Keng Kang I, Khan Chamkamorn, Phnom Penh, Cambodia, email: tryr@who.int

Ms Elodie Jacoby, Consultant, Communication and Programme Management Officer, No. 61-64, Preah Norodom Blvd. (corner St. 306) Sangkat Boeung Keng Kang I, Khan Chamkamorn, Phnom Penh, Cambodia, email: jacobye@who.int

Ms Sreyleak Kheng, Assistant, No. 61-64, Preah Norodom Blvd. (corner St. 306), Sangkat Boeung Keng Kang I, Khan Chamkamorn, Phnom Penh, Cambodia, email: khengs@who.int

Dr Giulia Manzoni, Consultant, Intensification Plan Project, No. 61-64, Preah Norodom Blvd. (corner St. 306), Sangkat Boeung Keng Kang I, Khan Chamkamorn, Phnom Penh, Cambodia, email: giulia.manzoniwho@gmail.com

Mr Matteo Dembech, Technical Officer, No. 61-64, Preah Norodom Blvd. (corner St. 306), Sangkat Boeung Keng Kang I, Khan Chamkamorn, Phnom Penh, Cambodia, email: dembechm@who.int

Mr Harry Gibbs, Information Officer, No. 61-64, Preah Norodom Blvd. (corner St. 306), Sangkat Boeung Keng Kang I, Khan Chamkamorn, Phnom Penh, Cambodia, email: gibbsh@who.int