Meeting Report

EIGHTH MEETING OF THE GREATER MEKONG SUBREGION THERAPEUTIC EFFICACY STUDY NETWORK

28–29 October 2020

Virtual Meeting

World Health Organization
Western Pacific Region

WORLD HEALTH ORGANIZATION

REGIONAL OFFICE FOR THE WESTERN PACIFIC

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Convened by:

WORLD HEALTH ORGANIZATION REGIONAL OFFICE FOR THE WESTERN PACIFIC

Virtual meeting
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NOTE

The views expressed in this report are those of the participants of the Eighth 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 the Member States in the Region and for those who participated in the virtual Eighth Meeting of the Greater Mekong Subregion Therapeutic Efficacy Study Network from 28 to 29 October 2020.

CONTENTS

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

LIST OF ABBREVIATIONS

ABER	annual blood examination rate
ACPR	adequate clinical and parasitological response
ACT	artemisinin-based combination therapies
AFRIMS	the Armed Forces Research Institute of Medical Sciences
AL	artemether-lumefantrine
AM	intramuscular artemether
API	annual parasite index
AQ	amodiaquine
AS	artesunate
AS-AQ	artesunate-amodiaquine
AS-MQ	artesunate-mefloquine
AS-PY	artesunate-pyronaridine
AS-SP	artesunate+sulfadoxine-pyrimethamine
BMGF	Bill and Melinda Gates Foundation
eCDS	electronic Communicable Disease System
CHAI	the Clinton Health Access Initiative
CIOMS	Council for International Organizations of Medical Sciences
CMPE	Lao PDR Center for Malaria, Parasitology, and Entomology
CNM	Cambodian National Center for Parasitology, Entomology and Malaria Control
CQ	chloroquine
CSO	civil society organization
DDC	Thailand Department of Disease Control
DHA-PPQ	dihydroartemisinin-piperaquine
DHIS2	District Health Information System 2
DSME	digital solutions for malaria elimination
DVBD	Thailand Division for Vector Borne Disease
ECAMM	external competency assessment of malaria microscopists
ERAR	Emergency Response to Artemisinin Resistance
GLURP	*glutamate-rich protein*
GMS	Greater Mekong subregion
iDES	integrated Drug Efficacy Surveillance
IPT	intermittent preventive treatment
K13	*Kelch 13*
LLIHN	long-lasting insecticidal hammock net
LLIN	long-lasting insecticidal net
Lao PDR	Lao People’s Democratic Republic
MEDB	Malaria Elimination Database
MME	Mekong Malaria Elimination programme
MMP	mobile and migrant populations
MMS	malaria management system
MORU	Tropical Medicine Research Unit
MPAC	Malaria Policy Advisory Committee
MQ	mefloquine
MSP	*merozoite surface proteins*

NIMPE	Viet Nam National Institute of Malariology, Parasitology and Entomology
NIPD	National Institutes for Parasitic Diseases (China)
NMP	National Malaria Programme
NRA	national regulatory agencies
NTG	national treatment guidelines
PCR	polymerase chain reaction
G6PD	*glucose-6-phosphate dehydrogenase*
PHEOC	public health emergency operations centre
PMI	President's Malaria Initiative
PPE	personal protective equipment
PPQ	piperaquine
PQ	primaquine
PY	pyronaridine
QA	quality assurance
QC	quality control
RAI	Regional Artemisinin-resistance Initiative
RDMA	Regional Development Mission for Asia
RDSP	Regional Data Sharing Platform
RDT	Rapid Diagnostic Test
RSC	Regional Steering Committee
SLD	single low dose
SOP	standard operating procedure
TDA	targeted drug administration
TES	therapeutic efficacy studies
TICA	Thailand International Cooperation Agency
TQ	tafenoquine
WHA	World Health Assembly
WHO	World Health Organization

SUMMARY

On 28 and 29 October 2019, the World Health Organization (WHO) Mekong Malaria Elimination (MME) programme hosted the virtual Eighth Meeting of the Greater Mekong Subregion Therapeutic Efficacy Studies Network. Representatives from malaria control programmes in the Greater Mekong Subregion (GMS) Member States – Cambodia, China, the Lao People's Democratic Republic, Myanmar, Thailand and Viet Nam – attended the two-day workshop to monitor progress and review the results of therapeutic efficacy studies (TES) as well as to plan and implement future TES and integrated drug efficacy surveillance (iDES). Focal points from GMS countries as well as technical experts and partners also attended the meeting to review the current TES/iDES status and the efficacy of antimalarial drugs and to identify alternative artemisinin-based combination therapies (ACTs) for revision of national treatment guidelines (NTGs), as necessary.

The main discussion points included: challenges in countries regarding the shift from TES to iDES, drug efficacy updates and the changes in second-line treatments, data from molecular markers, the status of artemisinin resistance in the GMS, and guidelines on quality control (QC).

The key conclusions of the meeting included the following:

- **Overview of GMS malaria elimination:** From January to September 2020, the GMS countries demonstrated approximately a 61% decrease of *Plasmodium falciparum* cases and a 32% decrease of *P. vivax* cases compared to the same period in 2019. Implementation of activities continued as expected despite the coronavirus disease 2019 (COVID-19) pandemic. The relative importance of *P. vivax* cases is likely to increase as countries approach elimination; 82% of cases currently are *P. vivax.* Malaria is mostly concentrated in remote areas, where the disease disproportionately affects travellers to malaria-risk areas as well as mobile and migrant populations. Intensification strategies are being planned and implemented to reach those at highest risk, particularly in Cambodia, which is launching an aggressive approach.
- **Status of artemisinin resistance:** Data suggest that there has been no major increase in artemisinin partial resistance and multidrug resistance in the past year. GMS countries face a critical window of opportunity to eliminate *P. falciparum.*
- **National treatment guidelines (NTGs):** ACTs are available and have been tested for efficacy throughout the GMS. All countries are in the process of changing their second-line treatment to ACTs, in place of quinine. Thailand has adopted artesunate-pyronaridine (AS-PY) in two provinces along its border with Cambodia, and Viet Nam has begun using AS-PY in provinces reporting more than 10% failures of dihydroartemisinin-piperaquine (DHA-PPQ). Low-dose primaquine (PQ) for the treatment of *P. falciparum* malaria is included in all NTGs but is not fully operationalized in all countries.
- **Drug efficacy:** TES are the gold standard for monitoring drug efficacy to inform treatment policy. In 2020, the COVID-19 pandemic caused delays in activity implementation in some countries resulting in some additional challenges to follow-up.
    - **Cambodia:** Artesunate-mefloquine (AS-MQ) and AS-PY are demonstrating optimal efficacy. Piperaquine (PPQ) resistance has been detected in Cambodia, leading to policy change.
    - **Lao People's Democratic Republic:** Similar to Cambodia, AS-MQ and AS-PY are efficacious. The data on artemether-lumefantrine (AL) between 2019 and 2020 show that AL remains highly efficacious.
    - **Myanmar:** Data suggest that AL, AS-PY, DHA-PPQ and chloroquine (CQ) (for *P. vivax*) remain highly efficacious.
    - **Viet Nam:** National data suggest that AS-PY and AS-MQ are also efficacious, while DHA-PPQ shows lower levels of efficacy in at least four provinces. Molecular data indicate piperaquine (PPQ) resistance in Viet Nam.

- **Thailand:** DHA-PPQ is efficacious at the border with Myanmar, while AS-PY became the first-line treatment in the country's northeast due to high DHA-PPQ resistance. CQ (for *P. vivax*) showed efficacy in 2019 and 2020 compared to 2018 (Sisaket).
- **China (Yunnan):** No TES has been conducted in Yunnan since 2016 due to low malaria incidence. iDES formally started in Yunnan in areas bordering Myanmar in 2020.

- **Integrated drug efficacy surveillance:** In elimination settings, the collection of drug efficacy data can be shifted from a system comprising sentinel sites to an iDES system. Cambodia, China (Yunnan), the Lao People's Democratic Republic, Thailand and Viet Nam have piloted iDES, and Cambodia plans to scale up iDES in all pilot areas in 2021. Starting in 2021, the Lao People's Democratic Republic will be scaling up iDES in 125 elimination districts and incorporating it as a routine component of case investigations. Thailand has expanded iDES nationwide and used data to drive policy change.
- **Quality control monitoring:** Monitoring helps to identify gaps and challenges for improvement in TES and iDES implementation. In the past year, most countries were able to continue quality control activities, but travel restrictions due to COVID-19 has resulted in some delays.
- **Genetic markers:** The efficacy of AS-MQ and resistance to PPQ are confirmed by molecular markers in Cambodia, the Lao People's Democratic Republic, Thailand and Viet Nam. AS-MQ introduction is clearing KEL1/PLA1 strains (artemisinin and piperaquine resistant) in Cambodia. There is a potential risk of the spread of the triple mutant (piperaquine, mefloquine and artemisinin) associated with the implementation of triple ACTs. Amodiaquine (AQ) resistance is confirmed in Cambodia. Close monitoring, therefore, remains crucial for Cambodia.

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 Greater Mekong Subregion (2015–2030)*. 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 the iDES, develop recommendations for WHO and countries, and develop action plans for the next two years;

Specific objectives

2) to review (i) the implementation of the recommendations from the last TES meeting and (ii) the results of the recent TES and iDES;
3) 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
4) to develop GMS and country workplans and budgets for TES and iDES implementation and monitoring for 2021–2022.

2. PROCEEDINGS

2.1 Opening session

Dr Ailan Li, WHO Representative (Cambodia), delivered the welcome address. She emphasized that, despite the challenges brought on by the coronavirus disease 2019 (COVID-19) pandemic, the number of malaria cases had declined by 66% by October 2020 compared to the same period in 2019. Following the welcome address, Dr Luciano Tuseo, Coordinator, MME programme, provided a briefing of the meeting objectives, and Dr Aung Thi, Director of the National Malaria Control Programme, Myanmar, was elected as chair of the meeting.

2.2 Review of recommendations from 2018 and progress

Dr Maria Dorina Bustos, Technical Officer, WHO Regional Office for South East Asiathe , reviewed the recommendations for GMS countries and for WHO from the Seventh Meeting of the GMS TES Network in 2019, which encouraged countries to consider the following:

1) Continue monitoring the quality of TES implementation based on the WHO quality control (QC) checklist;
2) Continue efforts to strengthen microscopy quality assurance (QA) and molecular assays for achieving elimination;
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 subnationally;
4) Encourage the use of artemisinin-based combination therapies (ACTs) as second-line treatment, rather than quinine;
5) National malaria control programmes should work with country national regulatory authorities to identify bottlenecks and accelerate the registration process of antimalarials, as well as post-marketing surveillance for quality and safety.

In 2020, quality TES and monitoring are ongoing in five GMS countries: Cambodia, the Lao People's Democratic Republic, Myanmar, Thailand and Viet Nam. Although COVID-19 impacted the ability of WHO to conduct TES monitoring visits, local country office teams and the national malaria programmes (NMPs) continue to regularly conduct monitoring activities. Thailand was able to complete the External Competency Assessment of Malaria Microscopists (ECAMM) in November and December 2019; similar assessments were also planned for Cambodia and the Lao People's Democratic Republic but were cancelled due to the pandemic. Still, five national malaria laboratories from Viet Nam (3), Myanmar (1) and Thailand (1) participated in the ninth WHO regional external quality assessment of malaria laboratories. In November 2020, Thailand is scheduled to have two batches of the National Competency Assessments to strengthen the regional laboratories. Artesunate-mefloquine (AS-MQ) was tested in four provinces of Viet Nam, and in 2020 the country has revised its national treatment guideline (NTG) to use AS-MQ or artesunate-pyronaridine (AS-PY) in areas with a more than a 10% dihydroartemisinin-piperaquine (DHA-PPQ) failure rate. Thailand continues to use AS-PY in the two provinces bordering Cambodia and the Lao People's Democratic Republic. The Lao People's Democratic Republic is in the process of revising its NTG, with AS-MQ and AS-PY as the second-line drug. Cambodia plans to revise its second-line drug with AS-PY. In terms of the registration process of antimalarial drugs, the Lao People's Democratic Republic is in the process of registering AS-MQ and AS-PY. In Viet Nam, the National Institute of Malariology, Parasitology and Entomology (NIMPE), WHO and the Drug Administration of Viet Nam have held meetings to discuss the importation of AS-PY, AS-MQ and artesunate (AS) injections in the near future.

Following the recommendations from 2019, WHO has advised countries to use the updated WHO TES template and adhere to it to facilitate approval from the WHO Ethics Review Committee. WHO assists the countries when questions are raised by the Committee. WHO has also provided support for iDES implementation in the Lao People's Democratic Republic, Cambodia and Viet Nam. In Thailand, WHO has continued to provide technical assistance to improve local-level reporting and iDES data management and analysis. In the past year, WHO also supported countries to review and revise NTGs based on available TES data and other information. The Lao People's Democratic Republic, Myanmar, Thailand and Viet Nam all revised their NTGs while Cambodia has plans to do so in terms of its second-line drug. Thailand has printed and translated its revised NTGs to English.

WHO continues to support the full operationalization of revised NTGs with partners. WHO has provided technical assistance to Thailand to improve procurement logistics and supply chain systems for antimalarial drugs. WHO country offices in the Lao People's Democratic Republic and Viet Nam have also provided technical assistance for the revised NTGs.

2.3 Overview of the Mekong Malaria Elimination programme in the GMS

Dr Luciano Tuseo, Coordinator, MME programme, presented the progress updates in the GMS since the last TES meeting, the priorities in the Subregion and an overview of the MME programme. The country targets for malaria elimination in the GMS include: the elimination of all species of human malaria in Yunnan Province (China) by 2020 or earlier; the elimination of *Plasmodium falciparum* malaria in the Subregion by 2023; the elimination of all species of human malaria in Cambodia and Thailand by 2025; and the elimination of all species of human malaria in the GMS by 2030.

In terms of progress, the GMS has seen remarkable improvements in the past years. Malaria cases are now just concentrated in a few hotspots in the border regions of GMS countries. Cambodia has started implementing a radical cure of primaquine (PQ); however, there is a lack of implementation with a radical cure with PQ in the Lao People's Democratic Republic. From January to September 2020, *P. falciparum* and mixed cases have decreased by 67% in comparison to the same period in 2019. Similarly, *P. vivax* cases have decreased by 32% in the first nine months of 2020 when compared to 2019. From January to September 2020, approximately 82% of all cases were *P. vivax.* The relative importance of *P. vivax* cases is likely to increase as countries reach elimination.

The priorities for MME in the GMS include:

1) Targeting high-risk populations such as forest goers in remote areas and mobile and migrant populations. Most malaria transmission happens in the forest, but there are limited resources including health staffing. To reach remote populations, WHO advocates transitioning from village malaria workers to mobile malaria workers and from passive case detection to active case detection.

2) Monitoring drug efficacy and updating/implementing NTGs, including replacing ineffective first-line drugs, identifying second-line drugs and implementing *P. vivax* radical cure.

3) Improving surveillance and scaling up elimination phase activities. Elimination activities (case and foci investigation) are ongoing in all GMS countries. The WHO MME programme is going to conduct a Regional Workshop on Adoption and Implementation of WHO Policy Guidance on Malaria Elimination on 26 and 27 November 2020 to bring together GMS countries to discuss best practices in malaria elimination and define the steps needed in the GMS to eliminate malaria and obtain malaria-free certification.

4) Implementing more aggressive approaches, which include the last mile to *P. vivax* and malaria elimination.

Dr Tuseo described the synergetic approach to accelerate malaria elimination in active foci in Cambodia. The Cambodian response is based on receptivity and vulnerability scores resulting from foci classification. This approach includes a combination of targeted drug administration (TDA) and intermittent preventive treatment for travellers to malaria risk areas to interrupt transmission of falciparum malaria and accelerate malaria elimination. The programme will also top up distributions of long-lasting insecticide-treated nets (LLINs), long-lasting insecticide-treated hammock nets (LLIHNs) and repellents to ensure vector control measures are in place. Lastly, house-to-house fever screening will be conducted every week to ensure every person with a fever is tested for malaria and treated if positive.

The MME programme recently submitted two grants to the Global Fund's Regional Artemisinin-resistance Initiative (RAI) 3E. The goal of these packages is to a) interrupt the transmission of *P. falciparum* in all areas of multidrug resistance in the GMS by 2023; and b) in areas where malaria transmission has been interrupted, maintain malaria-free status and prevent reintroduction. This will be achieved through the following:

1) Implementing the intensification plan approach of reducing the malaria burden among forest goers/travellers to malaria-endemic areas and hard-to-reach populations in all five GMS countries to accelerate malaria elimination.

2) Providing technical support to the NMPs and implementing civil society organizations in collaboration with local authorities in the five GMS countries to strengthen their capacity to support the coordination and implementation of operational activities and manage elimination surveillance systems.

3) Monitoring the malaria elimination progress on a monthly basis within and across the five GMS countries to address national and cross-border challenges to elimination through the Malaria Elimination Database, or MEDB.

4) Strengthening the overall capacity of all national programmes to meet the WHO eligibility requirements for malaria-free certification by 2023.

In terms of communications and advocacy, the MME programme will increase its emphasis on raising awareness of the existence and impact of the malaria elimination activities in the GMS. In the context of COVID-19, malaria must retain a prominent position in national agendas in order to receive ongoing support. Key focus areas will be to highlight success stories and innovative approaches from all GMS countries. The MME programme will communicate milestones to drive continued interest in regional progress towards the 2030 targets. Success stories from the last mile of malaria elimination will be shared through global, national and regional platforms to support advocacy efforts. In addition, the MME programme will promote the achievements of malaria efforts to emphasize their impact and will continue to ensure the systematic flow of communication and data among partners.

2.4 Updates on global antimalarial drug resistance, including partial resistance to artemisinin and partner drugs in the GMS

Dr Pascal Ringwald, Coordinator, WHO Global Malaria Programme, provided an overview of global antimalarial drug resistance, including partial resistance to artemisinin and partner drugs in the GMS. To respond to malaria drug resistance, countries need systems that can both detect changes in how well the recommended treatment is working and implement changes in policy when needed. TES are the gold standard for monitoring drug efficacy to inform treatment policy. In countries implementing malaria elimination activities (where case numbers are low), efficacy can be monitored by iDES. Additional information to confirm that treatment failure is linked to drug resistance can be gathered from molecular markers, in vitro and ex vivo studies.

Key definitions relating to drug resistance:

- Antimalarial resistance is the ability of a parasite strain to survive and/or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended but within tolerance of the subject.
- Artemisinin resistance is delayed parasite clearance following treatment with an AS monotherapy or with an ACT.
- Multidrug resistance is resistance to more than two antimalarial compounds of different chemical classes. This term usually refers to *P. falciparum* resistance to chloroquine (CQ), sulfadoxine-pyrimethamine, and a third antimalarial compound.
- Treatment failure is the inability to clear parasites from a patient's blood or to prevent their recrudescence after the administration of an antimalarial. Many factors can contribute to treatment failure, including incorrect dosage, poor patient compliance, poor drug quality, and drug interactions and resistance. Most of these factors are addressed in TES. It should be emphasized that treatment failure is not equal to resistance, and it is not possible to measure the poor reaction of drugs through these methods.

P. falciparum resistance has posed the greatest challenge for ACTs. The ACTs currently recommended for the treatment of uncomplicated *P. falciparum* malaria are AL, artesunate-amodiaquine (AS-AQ), artesunate-mefloquine (AS-MQ), artesunate+sulfadoxine-pyrimethamine (AS-SP), DHA-PPQ, and

AS-PY. In most of the world, these antimalarial drugs are highly efficacious. However, *P. falciparum* resistance in the GMS does pose a challenge.

In the last decade, the GMS conducted almost 200 TES. The most tested are DHA-PPQ with 88 studies conducted between 2010 and 2019. Inside the Subregion, AL is considered borderline, as it works in some areas but not in all. It currently works but it is unclear how long it will remain efficacious in the Lao People's Democratic Republic and Thailand. AS-AQ was first tested in Viet Nam and later in Cambodia, but it was found not to work in Cambodia. There have been failures in Cambodia and Thailand with AS-MQ as a first-line drug. This led to policy changes, and DHA-PPQ was used as a replacement in Cambodia, Thailand and Viet Nam. Following this, there was a reversal of AS-MQ resistance. AS-PY efficacy is high, although some years ago there were failures in Cambodia. AS-PY is currently efficacious in both Cambodia and Viet Nam. However, there have been documented issues with high treatment failures of DHA-PPQ in Cambodia, Thailand and Viet Nam. AS-MQ treatment for the PPQ-resistant parasites that were carrying the K13 mutation has reduced cases of treatment failure in Cambodia.

Once the genetic changes associated with resistance are identified, drug resistance can be confirmed and monitored with molecular techniques. Good molecular markers exist for artemisinin, piperaquine and mefloquine. At this stage, no molecular markers exist for lumefantrine, pyronaridine (PY), AQ and quinine.

Artemisinin (partial) resistance is associated with delayed parasite clearance. In TES, this is seen as an increase in patients with day 3 parasitaemia. Artemisinin resistance only affects the ring stages of *P. falciparum* and is found to be associated with K13 mutations. Validated molecular markers of artemisinin (partial) resistance have been detected outside the GMS. In Myanmar, the main molecular markers are F4461, M4761 and R561H. There was likely artemisinin resistance in China, but the country could eliminate malaria despite the presence of the drug-resistant parasites. In Thailand, the primary markers are N458Y1, R539T, P553L and C580Y. In Viet Nam and Cambodia, Y493H and I543T molecular markers are more prevalent.

In the GMS, most mutations occur in C580Y and there is a wide variation of mutations. In Cambodia, C580Y mutations have been replaced by wild types and Y493H, which appears to be connected to the adoption of AS-MQ. Validated molecular markers of artemisinin (partial) resistance have been detected outside the GMS. The C580Y and R561H parasites have appeared in foci globally and are a concern for malaria elimination efforts.

Dr Ringwald reiterated that, even if a high prevalence of mutants is detected in a site, the efficacy can remain extremely high as long as the partner drug is efficacious. This fully supports the argument that a low dose of DHA-PPQ should be provided in all countries of the GMS in order to reduce the gametocide carriage and avoid further spread of drug-resistant parasites.

In terms of *P. vivax,* CQ remains efficacious in many countries. However, *P. vivax* CQ treatment failure on or before day 28 or prophylactic failure has been observed in a number of countries. Confirmation of true CQ resistance requires additional studies of drug concentrations in blood. Therefore, it is necessary to continue to track the efficacy of CQ for *P. vivax*; ACTs (apart from possibly AL) are a very good option in the event of treatment failure.

To conclude, Dr Ringwald reminded all participants that all country data are available in the WHO database.

2.5 Updates from GMS countries on the status of TES or iDES

2.5.1 Cambodia

Dr Rithea Leang, TES Principal Investigator, National Center for Parasitology, Entomology and Malaria Control (CNM), provided an update on the country's progress in TES and iDES. In Cambodia, the average number of cases spiked in 2017 and 2019 and have otherwise decreased. Between January and June 2020, there were 5000 fewer *P. falciparum* and mixed cases when compared to the same period in 2019. The 2020 incidence rate for *P. falciparum* is 0.03 cases per 1000. *P. falciparum* and mixed cases are concentrated in the north and centre of the country. The current malaria policy for uncomplicated malaria is AS-MQ for the first-line treatment and AS-PY for the second-line treatment. For severe malaria cases, an intravenous injection of AS is provided. The last revision in Cambodia's NTGs was in 2016 when the country shifted from DHA-PPQ to AS-MQ.

Dr Leang presented a brief overview of changes in national malaria drug policies in Cambodia. In 2016, TES for *P. falciparum* cases were conducted in Stung Treng, Ratanakiri, Kampong Speu, Kratie, Mondulkiri and Pursat. The TES found that the efficacy of DHA-PPQ adequate clinical and parasitological response (ACPR) was 70% in Stung Treng and 83% in Ratanakiri. The ACPR rate of AS-MQ was 100% in Kampong Speu and Kratie. The efficacy of AS-AQ was below the 10% threshold, with ACPR rates of 77% in Mondulkiri and 86% in Pursat. These findings confirmed AS-MQ efficacy in two sites while AS-AQ was failing, and there was a high DHA-PPQ failure in the northeast of Cambodia.

The TES results from 2017 demonstrated full efficacy of AS-MQ *P. falciparum* cases in three sites (Kampong Speu, Stung Treng and Pursat). AS-PY also demonstrated high efficacy in two sites: Ratanakiri (ACPR of 96.7%) and Mondulkiri (ACPR of 98.3%).

In 2018, AS-MQ for *P. falciparum* cases was investigated in three sites (Kratie, Mondulkiri, and Ratanakiri) and AS-PY in two sites (Kampong Speu and Pursat). AS-MQ demonstrated 100% efficacy in Kratie and Mondulkiri, and 98.1% in Ratanakiri. AS-PY demonstrated 100% efficacy in Pursat and 98.7% in Kampong Speu. Based on these reported findings, AS-MQ was highly effective for *P. falciparum* patients in almost all sites of Cambodia. For *P. vivax* cases, AS-PY and AS-MQ were fully efficacious after 28 days.

In 2019, a TES of AS-MQ for *P. falciparum* cases was conducted in Kampong Speu (two sites), Kratie, Mondulkiri, Pursat and Ratanakiri. The study found that AS-MQ demonstrated high efficacy in Ratanakiri and two sites of Kampong Speu (ACPR of 100%). In Pursat, the ACPR of AS-MQ was 88%.

The 2020–2021 TES will investigate AS-MQ for *P. falciparum* and *P. vivax* in Kampong Speu and Stung Treng and for AS-PY in Kampong Speu, Pursat and Ratanakiri.

Dr Leang noted that the current challenge for TES has been the historical low *P. falciparum* and *P. vivax* incidence rates in the country and also highlighted that a best practice from the field included active screening in communities, solid communication with village malaria workers. Dr Leang concluded that AS-MQ as a first-line treatment in Cambodia continues to show optimal efficacy after four years of close monitoring. In 2020, Cambodia will complete operational research on qualitative G6PD testing of male and *P. vivax* patients with the CareStart Rapid Diagnostic Test (RDT) and 14 days of PQ for tested non-deficient patients in four provinces. In 2021, a country-wide study will be concluded on quantitative G6PD testing of male and female *P. vivax* patients with a SD Biosensor and 14 days of PQ for tested non-deficient patients.

During the discussion, Dr Leang noted that Cambodia has already completed one pilot iDES in Takeo province. The CNM plans to roll out iDES in all former TES sites.

2.5.2 Lao People's Democratic Republic

Dr Keobouphaphone Chindavongsa, representative from the Center for Malaria, Parasitology, and Entomology (CMPE), provided an update on the progress of the Lao People's Democratic Republic in terms of malaria elimination. In 2020, malaria cases were concentrated in the southern part of the country.

The CMPE recommended AS-MQ as the new second-line ACT for all forms of uncomplicated malaria in the NTG. The current malaria policy for uncomplicated *P. falciparum* malaria cases is a single low dose (SLD) of AL+PQ for the first-line treatment and quinine and doxycycline and of PQ (SLD) for the second-line treatment. For severe *P. falciparum* malaria cases, an artemisinin injection and AL+PQ (SLD) is provided for the first-line treatment. The second-line treatment is a quinine infusion and AL+PQ (SLD). Pregnant *P. falciparum* malaria cases receive an oral dose of quinine in the first trimester and artemether/lumefantrine in the second and third trimesters.

Uncomplicated *P. vivax* malaria cases receive AL + PQ and a G6PD test during the first-line treatment. An oral dose of CQ+PQ and a G6PD test are administered as a second-line treatment. Pregnant *P. vivax* malaria cases receive an oral dose of CQ in the first trimester and Coartem in the second and third trimesters.

Dr Chindavongsa presented TES results from 2013 to 2019 in two southern provinces (Champasak and Salavanh). In 2018–2019 in Champasak, AS-MQ demonstrated 100% efficacy and in Salavanh, AS-PY also demonstrated 100% efficacy. The Champasak samples demonstrated a K13 mutation rate of 75% (C580Y and C447R), while the Salavanh samples demonstrated a K13 mutation rate of 13.8% (C580Y). Results from 2014 and 2016 indicated that AL presented decreasing therapeutic efficacy (ACPR < 90%) as first-line drug for *P. falciparum* malaria, but the sample numbers were too low to make conclusions.

AL has been investigated since July 2019 in three provinces (Champasak, Salavanh and Savannakhet). The results from the current TES for AL (expanded to end 2020) will inform a full update of the NTGs, but results so far point to the continued efficacy of this drug for *P. falciparum* malaria (ACPR 97%) and *P. vivax* malaria (ACPR 100%).

In 2019 and 2020, iDES has been piloted in Luang Prabang and Phongsaly provinces. Luang Prabang is a very low-endemic area with 55 malaria cases reported in 2017. Phongsaly province is the highest malaria-endemic province with 82 malaria cases detected in 2018. Recent data showed that parasites from Phongsaly carried the C580Y K13 mutation. In 2019, the iDES recruited three *P. vivax* malaria cases; by October 2020, 14 *P. vivax* malaria cases had been recruited. Preliminary results suggest 100% efficacy of this treatment against *P. falciparum* and *P. vivax* malaria.

The CMPE conducts internal and external monitoring. Cases are monitored through a customized Google sheet. However, the accuracy readings from the first month (M1) in some district hospitals is a concern. In addition, the reading of M2 slides is often prolonged. The CMPE has noted a discrepancy of 53% to 100% between M1 an M2 readings. During M3, the CMPE validates data on a monthly basis. Monitoring of M2 directly to the TES laboratory is not allowed unless experts participate in a mission of principal investigators.

One of the major challenges is the reduction of malaria cases in study sites. To mitigate this issue, the CMPE monitors cases in the District Health Information Software DHIS2 database and provides distance support to the physical asset management and digital asset management teams to recruit as many patients as possible. Most cases detected at the health centre and village levels are in remote areas. These areas can be located far away from district hospitals. Dr Chindavongsa explained that the CMPE supports advocacy and networking with local administrative authorities to convince people to participate in TES. Given low numbers of *P. falciparum* in 2020 and difficulties referring patients from very remote highest-burden areas, however, it will be difficult to hit 2020 TES targets for *P. falciparum*.

Another issue is related to the high turnover of trained staff. To minimize disruptions, the NMP conducts on-site training during internal monitoring missions and maintains distance monitoring. Other

challenges in the Lao People's Democratic Republic include maintaining high-level microscopy at sentinel sites and coordination between health centre staff and district hospital staff for case referrals. This issue can be addressed by refresher training courses for district microscopists.

Dr Chindavongsa highlighted an ongoing study on the efficacy of AL with the Institut Pasteur du Laos. The study focuses on the same sites in Champasak, Salavanh and Savannakhet as the ongoing TES. The objective of the study is to collect blood samples from malaria patients that qualify for the TES in the field study sites for laboratory analysis to identify and map resistant markers in AL, the artemisinin partner drug. By October 2020, 73 samples had been collected.

Dr Leang concluded that preliminary TES results for AL indicate its continued efficacy in the Lao People's Democratic Republic for treating *P. falciparum* and *P. vivax* malaria.

During the discussion, Dr Tuseo and Dr Ringwald noted that issues in reaching enough numbers for TES will become more common as countries continue to eliminate malaria. Dr Ringwald noted that countries need to integrate efficacy into their surveillance systems. It is recommended to collect filter papers as they provide indirect evidence of how the parasite is resistant to some of the molecular markers. Since validated molecular markers do not exist for all drugs, collecting filter papers is a mitigated way of tracking drug resistance.

2.5.3 Myanmar

Dr Aung Thi, Deputy Director, National Malaria Programme, and Dr Kay Thwe Han jointly presented updates from Myanmar. Dr Aung began with a presentation of the COVID-19 situation in the country. In Myanmar, 290 townships (of 330 total) are malaria endemic. A total of 56 411 cases were reported in 2019, of which 60% were *P. vivax*. From January to August 2020, malaria cases reduced by 17% in comparison to the same period in 2019. In July 2020, there was a 7% increase in *P. vivax* cases due to unusual seasonal malaria transmission. Overall, 20 townships account for 81% of all malaria cases. The malaria burden lies along the western and eastern borders, which contain conflict and non-government-controlled areas. Intensification plans are under way to flatten the curve in 12 high-burden townships.

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 alternate ACT+PQ. For treatment failure after 28 days, patients are prescribed alternate 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. falciparum* malaria was recently revised, and cases receive CQ+PQ for 14 days for all levels. However, PQ is not given for *P. malaria.*

Dr Kay presented information on the TES sites. TES for 2018 and 2019 were mostly located in border areas, with many sites close to coal mines. The 2018 TES investigated AS-PY for *P. falciparum* cases in Myawaddy (Kayin) and Kawthoung (Thanintharyi). In 2019, AL and DHA-PPQ for *P. falciparum* were investigated in Tamu. Results from the 2019 TES demonstrate full efficacy of DHA-PPQ and 96.7% (ACPR) of AL for *P. falciparum* patients in Tamu and Tanintharyi. In 2020, TES investigated AL and DHA-PPQ for *P. falciparum* cases and CQ for *P. vivax* cases in Buthidaung, Rakhine State. The ACPR findings indicate full efficacy of AL, 98% efficacy of DHA-PPQ and 96% efficacy of CQ.

Dr Kay also described several challenges, such as inadequate numbers of cases, financial limitations to access to hard-to-reach areas, security issues in conflict areas, language barriers and shortage of technical staff (especially young professionals). She also noted that there had been a delayed arrival of molecular reagents due to COVID-19 travel restrictions.

COVID-19 has caused additional challenges for malaria elimination. Travel restrictions have meant that active case detection surveys have stopped. Channels to transport malaria supplies, collected blood samples and case record forms have been distorted. The malaria screening of fever cases has stopped, and all patients with a fever are directed to fever surveillance clinics. Research teams and malaria volunteers are trained for universal precaution only; therefore, trials were suspended to protect field workers from COVID-19 infection.

Dr Kay concluded the presentation by noting that the monitoring of artemisinin resistance is crucial for countries that have entered the elimination phase. TES indicate that the current ACTs and partner drugs are working well in Myanmar, but monitoring of ACT efficacy is strongly recommended in border, hard-to-reach and conflict-affected areas. Lastly, the molecular surveillance of artemisinin and partner drugs is worth continuing.

2.5.4 Viet Nam

Dr Bui Quang Phuc, representative from the Viet Nam National Institute of Malariology, Parasitology and Entomology (NIMPE), presented the TES findings for Viet Nam. Between 2010 and 2019, the number of confirmed malaria cases decreased by 71%. There were no malaria related deaths in 2019. In 2019, most cases were reported from the Central Highlands and southern provinces.

The current malaria guideline for uncomplicated *P. falciparum* or mixed *P. malariae* or *P. knowlesi* cases is DHA-PPQ + a single dose of PQ. Uncomplicated *P. falciparum* or mixed *P. vivax, P. ovale* cases receive DHA-PPQ+PQ for 14 days. Uncomplicated *P. vivax, P. malariae, P. ovale* or *P. knowlesi* cases receive CQ + PQ for 1 or 14 days. *P. falciparum* cases in Binh Phuoc, Dak Nong, Dak Lak and Gia Lai where there is evidence of resistance to DHA-PPQ receive AS-PY+PQ or AS-MQ (for patients > 7 years old and > 20 kilograms) or DHA-PPQ+PQ (for patients < 7 years old and < 20 kilograms). *P. falciparum* cases exhibiting failure to ACTs receive quinine + doxycycline (for seven days); or quinine + clindamycin (for seven days). *P. vivax* cases failing with CQ receive ACTs. Pregnant malaria cases receive quinine and clindamycin (*P. falciparum*) or CQ (*P. vivax)* in the first trimester, and all cases receive DHA-PPQ or other ACTs in the second and third trimesters. All complicated cases receive an injection of AS/quinine.

TES results from 2019 demonstrate full efficacy of AS-MQ in Binh Phuoc and Dak Nong. DHA-PPQ continued to demonstrate low efficacy, with an ACPR of 27.7% in Dak Lak (without PCR correction), 84.2% in Gia Lai and full efficacy in Khanh Hoa, respectively. TES results from 2020 indicate full efficacy of AS-MQ for *P. falciparum* in Gia Lai and Dak Lak as well as full efficacy of AS-PY in Dak Nong.

From July 2020, Viet Nam started pilot iDES monitoring in Phu Yen. By October 2020, the CMPE had enrolled 12 *P. falciparum* and eight *P. vivax* cases. In the future, Viet Nam would like to open iDES in eastern provinces where there are more hotspots.

Current challenges are compliance in TES after 42 days and follow-up with forest goers. Other challenges include reduced cases for sampling in TES and many overlapping malaria activities in the same sites. One of Viet Nam's key successes has been close collaboration with the government and the private sector for recruiting patients and obtaining funding for a prolonged TES.

During the discussion, Dr Ringwald noted that WHO can support in requests to the Ministry of Health to change sentinel sites for the TES. He stressed the need to change TES provinces or districts to accurately cover hotspots. Dr Tuseo recommended that all countries move to AS-PY as a first-line drug as very few children are affected by malaria.

2.5.5 China (Yunnan Province)

Dr Fang Huang, Principal Investigator, the National Institutes for Parasitic Diseases (NIPD), provided an update on the country's progress in TES and iDES. China is approaching malaria elimination in 2020. Between January and September 2020, there were 106 imported *P. falciparum* cases, seven *P. vivax* cases and six other cases.

The National Health Commission has recommended multiple programmes for both *P. falciparum* and *P. vivax.* The current malaria treatment policy for *P. falciparum* is ACTs + PQ, DHA-PPQ, AS + AM or AS-PPQ. DHA-PPQ is the most commonly administered treatment. The policy for *P. vivax, P. ovale* and *P. malariae* is CQ + PQ (eight days) or PPQ/PY/ACTs for CQ failure. The provision of CQ + PQ (eight days) is different to WHO guidelines. Severe malaria cases receive AS, artemether and PY followed by an ACT.

All the TES sites are along the border of Myanmar's Kachin state. The TES was supported by the MME programme until 2016. From 2015 to 2018, patient numbers were low but there was evidence of resistance among some patients.

Due to the low patient numbers, China designed a pilot iDES framework for Yunnan Province. In 2020, the iDES of CQ was implemented in 2020 in three sites (Dehong Dai and Jingpo Autonomous Prefecture, Baoshan and Chuxiong prefectures). The studies were postponed due to the increased focus on malaria elimination. Only *P. vivax* patients were included in the iDES. The work is still ongoing, and all imported cases are screened and included in the iDES.

Dr Fang noted that China is not as familiar with iDES studies and requires technical support from WHO at all levels. The NIPD would like to see best practices to understand how to integrate iDES into standard surveillance activities. The last challenge noted was the need to maintain full engagement in malaria surveillance while fighting the COVID-19 pandemic.

During the discussion, Dr Fang noted that half of *P. falciparum* cases are from Southeast Asia and the other half are from Africa. Most *P. vivax* cases are from Myanmar.

2.5.6 Thailand

Mr Rungniran Sugaram, representative from the Division for Vector Borne Disease (DVBD), presented the TES findings for Thailand. Since 2015, Thailand has reduced the total number of malaria cases by 76% and the total number of *P. falciparum* cases by 96%. Active foci have reduced by 61% from 1553 to 605 clusters. From October 2019 to September 2020, most remaining cases were *P. vivax* (92%) and no deaths were recorded.

The NTGs for uncomplicated *P. falciparum* cases is DHA-PPQ for three days + a single dose of PQ for the first-line treatment (except in Sisaket and Ubon Ratchathani where patients receive AS-PY for three days + a single dose of PQ). For the second-line treatment, the available ACTs are either AS-PY for three days + a single dose of PQ, AL for three days + a single dose of PQ or AS-MQ for three days + a single dose of PQ. For non-ACTs, the DVBD prescribes quinine+clindamycin/doxycycline/tetracycline for seven days + single dose of PQ or atovaquone-proguanil for three days + a single dose of PQ.

The NTG for medical doctors and NTG for public health officers are under development. The updated 2019–2020 NTG for uncomplicated *P. vivax* or *P. ovale* cases is CQ for three days + a low dose of PQ for 14 days as the first-line treatment. For the second-line treatment, patients receive DHA-PPQ for three days + a low dose of PQ for 14 days. *P. malariae* or *P. knowlesi* cases receive CQ for three days during the first regimen and DHA-PPQ for three days during the second regimen. Mixed *P. falciparum* with *P. vivax* or *P. ovale* receive DHA-PPQ for three days + a low dose of PQ for 14 days. Mixed *P. falciparum* with *P. malariae* or *P. knowlesi* are administered DHA-PPQ for three days + a single dose of PQ.

Severe malaria cases receive an AS injection within the first 24 hours, followed by a first or second regimen when the patient can take medicine, with supportive care. During the second-line treatment, the patients receive a quinine injection within the first 24 hours followed by a first or second regimen when the patient can take medicine, with supportive care. Pregnant malaria cases receive quinine and clindamycin for seven days or CQ for three days in the first trimester and DHA-PPQ (three days) or CQ (three days) in the second and third trimesters.

Thailand started its TES for AS-PY in Sisaket in June 2020; by October 2020, no cases had been enrolled. The results for molecular marker data collected from iDES in 2019 indicate that for K13 samples, 20 of the 29 samples were wild type. For pfpm2 and pfmdr1 copy number, none of the total samples (15) showed an increase in pfpm2 or pfmdr1 copy number.

The DVBD shared the iDES results from 2018 to 2019. In 2019, 5684 cases were enrolled in the iDES; by October 2020, 4244 cases had been enrolled. Overall, the adherence to NTG is improving over time. Follow-up rates dramatically improved in 2020, resulting in many more patients presenting for at least one follow-up visit compared to the previous year's rates. In 2020, there were very few *P. vivax*

recurrent cases (positive tests on day 14 or 28) that had been prescribed CQ+ PQ. Among the *P. vivax* patients suspected of relapse/infections, 17 were in Tak, nearly all of which were in Tha Song Yang district, and five were in Sisaket. Four of these patients in Tak and Sisaket presented for sequential follow-up visits with persistent *P. vivax* on days 60 and 90.

In 2020, the overall efficacy (not PCR-corrected) of *P. falciparum* cases that had been prescribed DHA as part of standard operating procedures (prescribed CQ + PQ) was 97.1%. In 2020, the national laboratory received 217 cases collected by real-time PCR. Out of these, 44 cases were confirmed *P. falciparum* cases. The K13 marker, pfplasmepsin2 and pfmdr1 copy numbers from these samples are pending.

A major challenge for iDES has been treatment compliance and completion of follow-up. Other challenges include improving the quality of blood sample collection, regular supervision and monitoring in the field, and capacity-building (such as maintaining skills in low-burden settings, supporting data management and analysis, and collecting and processing biomarkers at subnational levels).

The programme has identified multiple ways forward: improving NTG compliance and follow-up rates by involving village health volunteers and capacity-building on iDES; introducing national standard operating procedures for malaria microscope diagnosis on website documents and video; integrating epidemiological data and laboratory data for analysis; triangulating routine iDES results with research studies; and considering how to address *P. vivax* treatment outcomes in Sisaket.

Overall, the programme has found iDES to be a timely and useful tool for monitoring drug efficacy. TES will be implemented when new or alternative antimalarial drugs are introduced. There are also clinical trials with other antimalarials: a TES for AL, tafenoquine (TQ) feasibility study and PQ seven-day feasibility study. Additional research areas include highly sensitive RDT feasibility, a qualitative method for G6PD testing (applied fluorescence spot test) and a quantitative method for G6PD testing (biosensor with TQ project). Molecular marker surveillance involves the Genome Project, Mahidol Oxford Tropical Medicine Research Unit (MORU) and the Armed Forces Research Institute of Medical Sciences (AFRIMS).

Following the presentation, Dr Ringwald asked why there was change in the efficacy rate of *P. vivax* cases in Sisaket in 2020 in comparison to 2018. Mr Sugaram noted that there was no change in approach in Sisaket and the province continues to use CQ + PQ. However, the province has lower than average follow-up rates, which may affect the data.

Dr Ringwald also asked for an update on AS-PY TES. Mr Sugaram responded that a TES was initiated in 2020, but there were no malaria cases so the sample size was not reached. Following this, the Ministry of Public Healthethics committee did not approve to extend the project.

2.6 Opening session of day two

Dr Tuseo opened the session of the second day and nominated Dr Nguyen Quang Thieu from Viet Nam as the chairperson. Dr Nguyen accepted the nomination and started the introductions for the agenda.

2.7 Different drug efficacy surveillance systems: routine TES and iDES in the context of elimination and importation

Ms Charlotte Rasmussen, Technical Officer, Global Malaria Programme, provided an overview of TES and iDES in the context of elimination and importation. She noted that TES are considered the gold standard for monitoring drug efficacy to inform treatment policy. They monitor the efficacy for both *P. falciparum* and *P. vivax*, recommended first- and second-line drugs, as well as drugs that need to be monitored prior to possible introduction into the treatment policy. TES are conducted in sentinel sites. A sentinel surveillance system is used when high-quality data are needed that cannot be obtained through an existing routine surveillance system of data collection. Repeated TES in a limited number of sites is adequate to collect consistent longitudinal data and document trends. WHO recommends that

TES are completed in sentinel sites at least once every two years. TES provide prospective evaluations of patients' clinical and parasitological responses to treatment for uncomplicated malaria. Depending on the drug, they can cover a period of 28 days (for AL, AS-SP, AS-AQ) or 42 days (for AS-MQ, DHA-PPQ). Different factors (such as reinfection, drug interactions, comorbidities, medical conditions or poor drug absorption) can cause parasites to not disappear or to reappear. The treatment is supervised and controlled to the extent possible. Molecular markers can help inform TES, and they include parasite genotyping to distinguish recrudescence and reinfection. This looks at merozoite surface proteins (MSP1, MSP2) and glutamate-rich protein (GLURP) marker genes.

The WHO TES template is available in English and French. The protocol meets the ethical requirement of the World Health Assembly/Council for International Organizations of Medical Sciences and has been cleared by the WHO Ethics Review Committee. It includes provisions for both QC and QA. The template includes an Excel spreadsheet for data entry. Ms Rasmussen highlighted that all studies need to be registered and cleared by an independent institute for research in biomedicine and the clearance is valid for one year only.

The TES protocol can be adapted according to transmission settings. The main purpose of the adaption of the standard protocol is to ensure that a minimum sample size is reached for a sentinel site. The TES provide data on treatment failure, day 3 parasitaemia and the presence of molecular markers. Treatment failure is measured according to the percentage of patients (available for analysis) without ACPR. This indicator is most commonly used to inform treatment policies. Day 3 parasitaemia is based on the percentage of patients three days after starting treatment that are found to have parasites.

Routine TES for *P. vivax* infections look at the efficacy and resistance to the treatment of the blood stage parasites. Concomitant treatment against liver stage parasites can increase efficacy of treatment against resistant blood stage parasites. Therefore, radical treatment is moved to day 28, if locally acceptable. A challenge with *P. vivax* studies is that it is not possible to distinguish between recrudescence, infection and relapse. Sufficient drug blood concentrations 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 parasitaemia would not be expected before day 28. Therefore, treatment failures by day 28 are often defined as *P. falciparum* cases.

One of the challenges with TES is that in areas with very low transmission, sample size is difficult to achieve. TES aims to achieve a certain sample size by enrolling patients in sentinel sites to determine treatment failures. TES is typically conducted by study teams, and good quality data can be gathered in most settings. In countries without sufficient total cases, the changing epidemiology makes planning studies difficult. Therefore, in countries with low case numbers, it is impossible to estimate the failure rate using TES.

When a country transitions from a strategy of reduction of transmission to an elimination strategy, this requires changes both in the malaria surveillance system as well as in the case management system. When systems are shifted from TES to iDES, the routine system can provide information on numbers and percentage of treatment failures. In these situations, iDES operations are more appropriate as they aim to measure the treatment efficacy of all cases in an area and they rely on data collected as part of routine systems. iDES should only be implemented in the context of elimination programmes where most of the required data are already being collected. The methods and data collected in iDES vary between countries depending on the systems in place and the resources available. The minimum data required are the confirmation that the patient took the drugs, and data for two points: day 0 and the end day (in the case of failure, another full follow-up period is needed).

WHO has developed a list of mandatory and recommended activities for iDES treatment. Mandatory activities include the supervision of treatment and activities to receive second-line treatment (supervised) in the case of treatment failure and follow-up for an additional period. It is recommended to provide hospitalization during treatment. In terms of follow-up, the minimum is the end date of the treatment, but additional days are recommended. As for the information collected, the mandatory information include the symptoms, species, and confirmation of parasitaemia and species. However,

many countries choose to collect additional information including information such as a parasitaemia count, gametocytaemia parasite and additional clinical symptoms. Mandatory activities for diagnosis include recording of symptoms, species by RDT, and/or microscopy by day 0 and microscopy at the end day. G6PD testing is mandatory for *P. vivax*. However, it is recommended that diagnosis on day 0 include either parasitaemia count and gametocytaemia by microscopy or a PCR test. Microscopy is recommended for follow-up as well as a PCR test on the end day. Lastly, mandatory molecular markers include reinfection/recrudescence, identification of origin and drug resistance markers. For all of these, it is recommended to measure the blood on day 0 (and on day of failure for reinfection/recrudescence markers).

In conclusion, Ms Rasmussen highlighted that it is important for iDES that NMPs continue to monitor both the numbers and the preventive treatment failures. In addition, it is crucial to look at different programmatic issues such as the supervision of treatment, the percentage lost to follow-up, if the second-line treatment is given and if the treatment failures were followed up.

2.8 Quality control in TES and iDES: implementation challenges

Dr Maria Dorina Bustos provided an overview of implementation challenges in the QC of TES and iDES. Monitoring drug efficacy is a global public good, and WHO's responsibility, findings and updates are stored in the global database on therapeutic efficacy of antimalarials. WHO has developed templates for QC monitoring, which include 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 with actions on recommendations.

Dr Bustos provided an overview of the elements in the pre-study and interim visit checklist, including general study information, study sites and site-specific information, study-specific information and conclusions.

During the preparation phase, common challenges in TES include developing protocols and providing the correct background information in adherence to TES template 2018 v1.5.4. Other challenges include the selection of study sites as annual trends change the available locations, which is particularly relevant to the GMS as low case numbers in sentinel sites mean that it is harder to recruit patients for TES. Another issue relates to delays in protocol review and approvals by national stakeholders and the WHO Ethics Review Committee. Administrative delays and late reports can also impact the release of funds. Lastly, it is crucial that trials are officially registered 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. Other issues include lack of consent or assent forms, especially in the case of children from the ages of 12 until the age of majority. Challenges with treatment include the lack of second-line drug for rescue treatment in some district hospitals and health centres (to refer patients), missing drug inventory and suboptimal drug storage conditions. Additional issues can arise in supervising treatment if a patient is not hospitalized. For *P. vivax* TES, there can also be challenges with compliance for the administration of PQ 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 local cultures/customs. Consequently, female minors and unmarried women are excluded from the efficacy study. 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.

Problems in the laboratory relate to the quality of the microscopic blood examination. Despite repeated refresher trainings, WHO has observed some poor-quality slides. This can result from poor slide preparation, over- or under-staining. WHO requires laboratory microscopies to cross-check logbooks with slides to prevent discrepancies in the slide reading. Other common challenges relate to the fact that

the microscopy logbook of M1 and M2 is on-site, which can mean late or irregular validation by M3. Regular training is needed for proper collection of dried blood spot, labelling and storage.

In terms of the genotyping malaria parasites, challenges include when the genotyping of msp1, msp2 and GLURP are done together and not sequentially. This confounds differentiating recrudescence from reinfection. Another common problem is timely assays as part of QC and the identification of molecular markers for antimalarial drug resistance. For QA/QC, 10% of molecular procedures are sent to the WHO-appointed reference laboratory and it is compulsory to sign a material transfer agreement between countries and the reference laboratory.

For data entry, common challenges in using the Excel data entry form include completing the study site and drug information, failing to enter information for cases that are lost to follow-up or withdrawn, and double data entry or validation from the first to second entry. A final issue includes entering PCR results once they become available from the reference laboratory.

In areas with very low transmission pursuing malaria elimination, the number of malaria cases are most often too low for the needed number of cases to be reached at sentinel sites. Therefore, the surveillance system should be strengthened to improve case detection, increase case reporting from all sectors (private and public), ensure that all patients receive the full recommended treatment (including a radical cure) and confirm a complete cure by following up patients at regular intervals to an end point. The strengthened surveillance system can be used to also collect and analyse data on drug efficacy. Thus, efficacy monitoring is shifted from using a sentinel site TES to relying on data collected via routine surveillance systems (iDES).

In iDES, the implementation of the surveillance system is key and requires resources for hard-to-reach mobile populations, border and remote areas. As countries move towards elimination, they aim for improving case detection and increasing case reporting from all sectors. Timely (online) data entry is needed at field sites and district hospitals. Issues arise when there is delayed referrals or information from hospitals to malaria staff despite 24-hour case notification. In addition, regular field supervision, monitoring and data analysis are always needed. 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 follow-up and there is a need to ensure that cases are followed up in case of treatment failure. Additionally, not all hospital-treated cases follow the NTGs and for non-hospitalized cases it is sufficient to ensure compliance to the treatment regime. Adherence to the NTG and drug availability at district and private hospitals requires the reorientation of young doctors and staff to updated NTGs. An inventory of stock levels of second-line ACT and AS or quinine should be available. All related staff should receive proper (re)training on the use of surveillance report forms, laboratory forms and standard operating procedures. In addition, standardized reporting forms should be linked to laboratory forms. At the peripheral level, especially in district hospitals and health centres, technicians often miss the day 0 or day of failure slide in database collection as well as the filter paper collection procedure.

2.9 Updates on Kelch 13, plasmespsin and other molecular markers for resistance in the GMS

Dr Benoit Witkowski, Head of Unit, Institut Pasteur du Cambodge, summarized data from the ongoing investigations of the Institut Pasteur. He presented information on the context of ACT resistance in Cambodia, summarizing an overview of the history of treatment failures and molecular markers. From 2017 to 2019, there has been a clear trend in western and eastern Cambodia of decreasing PPQ-resistant molecular markers coupled with increasing mefloquine (MQ)-resistant markers. In western Cambodia, there has been a gradual disappearance of the Plasmespsin2 and CRT mutations within the population. The data indicate that the KEL1/PLA1 parasite was impacted by the use of AS-MQ. Notably, the novel C580Y are genetically distant from the KEL1/PLA1. Therefore, the re-emergence of multidrug-resistant parasites in Cambodia is not an evolution of KEL1/PLA1 parasites.

While PPQ resistance has decreased since 2017, there has been a concurrent increase in MQ susceptibility. This can be explained by the fact that MQ in AS-MQ is clearing KEL1/PLA1 from the parasite population. PPQ- and MQ-resistant parasites indicate similar levels of artemisinin resistance.

However, PPQ-resistant parasites are more susceptible to PPQ, and MQ parasites are more susceptible to PPQ. The major detriment in parasite evolution in the GMS is the partner drug.

Since 2016, more than 430 patients have been included in the TES (AS-MQ), with three failures recorded. All of these were mefloquine resistant and exhibited the Y439H or R539T mutants. In Cambodia, no formal molecular marker has been identified with AQ resistance. All assumptions based on the African experience should be approached with caution. The success of AS-PY is due to the absence of cross-resistance with PY and PPQ+MQ. For now, AS-MQ efficacy is very good, but this needs to be monitored. If it continues to efficacious, it could be a relevant option for countries with KEL1/PLA1 circulation.

Dr Witkowski summarized four main conclusions. Firstly, there has been a disappearance of the *P. falciparum* CRT protein mutation in Cambodia. Secondly, AS-MQ is driving a decrease of PQ resistance. Thirdly, there is a re-emergence of PPQ resistance in Cambodia. There is an opposite effect to mefloquine. Dr Witkowski highlighted that there is now a narrow window to eliminate malaria, although triple mutant strains and AQ resistance are an ongoing reality. Lastly, AS-PY displays a very good therapeutic efficacy in Cambodia and PY susceptibility appears to be independent to resistance profiles that have been observed. The data suggest that AS-PY could be an interesting second-line option in the case of AS-MQ failure.

2.10 Review of challenges affecting effective management of malaria in the context of current pandemic situation

Dr Neena Valecha, Malaria Regional Adviser, WHO Regional Office for South-East Asia, summarized the challenges facing malaria elimination in the face of the COVID-19 pandemic, which has been characterized by a highly transmissible infectious process. When health systems are overwhelmed, both direct mortality from the epidemic and indirect mortality from treatable and vaccine-preventable conditions increase dramatically. Malaria treatment is one of the health services affected. Guidance on how best to tackle COVID-19 is being made available by WHO and other agencies and is being updated regularly. Analyses from the 2014–2015 Ebola outbreak suggest that the increased number of cases and deaths caused by measles, malaria, HIV/AIDS and tuberculosis attributable to health system failures exceeded cases and deaths from Ebola.

WHO conducted a key informant survey among health ministry officials in 105 countries across five WHO regions between May and July 2020 to assess the impact of the COVID-19 pandemic on up to 25 essential health services in countries. All services were affected, including essential services for communicable diseases, noncommunicable diseases, mental health, reproductive, maternal, newborn, child and adolescent health, and nutrition services. The most severely affected service delivery platforms were mobile services, often suspended by government, and campaigns, for example as used for malaria prevention or immunization. In the WHO South-East Asia Region, there was a 20–90% disruption in health services. Countries reported that disruptions were caused by reductions in outpatient care attendance owing to lower demand (76%), lockdowns (48%) and financial difficulties (33%). The most commonly reported factor on the supply side was cancellation of elective services (66%).

The COVID-19 situation remains stable in the GMS except in Myanmar where positive cases and deaths are increasing. Internal migration within the countries has increased from urban to rural settings. This has led to increased provincial cases. Partners have also reported changes in forest-going behaviour, which has affected malaria transmission. There has been a noticeable decrease in active surveillance, especially during lockdowns. Other challenges have included delays in bed net campaigns and indoor residual spraying, delays of training programmes, deference of surveys and TES, and stock-outs of drugs such as PQ in the case of China.

Dr Valecha highlighted a number of key achievements from GMS countries since the start of the pandemic. Malaria cases, especially *P. falciparum*, continued to decrease in the GMS, but unusual seasonal increases in *P. vivax* cases were reported in some countries. At the GMS country level, the response was prompt and consistent in the development of guidance documents or operational plans

adapting malaria interventions in the context of COVID-19. The Global Fund proposals are on track, and overall there were adequate stocks of RDTs, ACTs, PQ and personal protective equipment. Elimination activities, including case and foci investigation, are on track, and intermittent preventive treatment for forest goers has been launched in Cambodia. By the third quarter of 2020, TES, monitoring and evaluation, trainings and meetings are now being organized, including microscopy trainings.

The impact of the pandemic on service disruption has been variable across countries depending on the COVID-19 situation and malaria endemicity. While countries are engaged in slowing the spread of the disease and providing care to COVID-19 patients, there is a need to minimize the impact on health systems. Malaria is a disease that can be easily diagnosed and treated effectively; therefore, it should be ensured that malaria control efforts are not hampered. It is possible but currently unknown whether malaria and its consequences, especially severe anaemia, may increase severe COVID-19 risk or vice versa. Malaria elimination activities should continue to follow best practices for safety of health-care workers/study teams as per WHO recommendations and adapt according to local needs. Protocols should be put in place, and health workers need to be motivated, educated and protected. Non-essential exposure and gatherings should be avoided, and countries should work to overcome travel restrictions to maintain supply chain, logistics and information systems. Lastly, NMPs should ensure continued access to vector control measures with local safety protocols.

In conclusion, GMS countries should follow best practices in the prevention and control of COVID-19 as per WHO recommendations and ensure flexibility and rapid response to safely serve patients with malaria prevention and case management in areas affected by COVID-19. NMPs should continue to provide core preventive and case management interventions for malaria, even with the risk of COVID-19. Exceptional measures to control malaria may be needed to minimize increased disease and death arising from the COVID-19 pandemic. These measures should only be applied following careful consideration of the context. Lastly, the core structures and systems for malaria should be strengthened as a central element of the COVID-19 response.

2.11 Plenary discussions Q&A

Dr Kay confirmed that Myanmar has a plan to complete an external QC.

Dr Bustos from WHO responded that every blood sample that is leaving a country needs to be approved. WHO can provide a draft of the material transfer agreement to the NMPs. These should all be sent to Institut Pasteur du Cambodge which would provide prior approval, receive and process the sample.

Dr Ringwald reiterated the importance of the data from Dr Witkowski's presentation. The samples from the different countries which were analysed by Institut Pasteur du Cambodge indicate that malaria remains a treatable disease. Although antimalarial drug resistance remains a risk, it should not be overstated. The data from the Institut Pasteur du Cambodge's in vitro and molecular studies provide valuable information about drug efficacy in the GMS. Dr Witkowski noted that the Institut Pasteur has also tested the in-vitro double combination of PPQ+MQ versus parasites with MQ resistance. The findings indicated that MQ resistance itself is enough to make a parasite tolerant to PPQ+MQ. The Institut Pasteur du Cambodge is currently conducting an investigation on the mechanistic aspects of this reaction.

Ms Rasmussen noted that iDES protocols for the timeline of the delivery of the second-line drug are linked to NTGs. She also highlighted that G6PD testing in iDES is recommended, and it is always done for *P. vivax* cases. Although G6PD testing does not happen during iDES in certain areas, it should be linked to NTGs and should not be considered a separate study.

Dr Bustos stressed that the follow-up for mobile and migrant populations relies on the strategies created by NMPs. During iDES, countries should try their best to complete at least a second or third follow-up visit with mobile and migrant populations. NMPs should follow guidelines and strategies to take into account to movements of different migrant populations.

Ms Rasmussen stated that iDES should not be a direct substitute for TES. iDES are complicated and resource intense but are possible for countries that are really focusing on elimination. It requires effort to train staff for a low number of cases and should be done where there are dedicated slides. There are ways to manage some of this process in a more flexible way. iDES can help elimination guidelines as it integrates follow-up into the elimination efforts.

Dr Bustos stated that the follow-up for iDES of *P. vivax* is on a weekly basis until day 28, then another follow-up on day 60 or 90. If NMPs want to monitor the effect of relapsing PQ, this is measured on day 60 or 90. It is recommended to follow up after three months but it depends on the resources in the country.

3. PRESENTATION OF COUNTRY PLANNING AND BUDGET FOR TES, IDES AND MOLECULAR MARKERS

3.1 Cambodia

For 2021–2022, Cambodia will conduct TES in eight sites, testing AS-MQ in four sites (Pursat (2), Kampong Speu and Kratie) and AS-PY in four sites (Ratanakiri (2), Pursat and Kampong Speu). In 2021, iDES will continue and Cambodia will focus on strengthening the surveillance system and ensuring the second follow-up for treatment failures.

3.2 Lao People's Democratic Republic

In 2021–2022, the Lao People's Democratic Republic will undertake TES for AL in three sites (Attopue, Salavanh and Savannakhet), and in 2021 for AS-PY in three sites (Champasak, Attapeu and Savannakhet). The country will expand iDES from two provinces (Phongsaly and Luangprabang) to all elimination provinces (13). In the first quarter of 2021, the updated malaria elimination strategy will be disseminated which includes a database and tracking system, and surveillance systems. The improvements to the national QA policy will be launched nationwide in the first quarter of 2021, and the national treatment policy is being improved. The country will ensure a second round of follow-up for treatment failures.

3.3 Myanmar

In 2020, the TES sites to be selected in Myanmar will be in the eastern and western borders, which are endemic for *P. vivax* and *P. falciparum.* Drug studies are currently being used for treatment (AL, DHA-PPQ, CQ). The TES sites planned for 2021 are Homalin in Sagaing state (AL and CQ), Moumak, Mabein in Northern Shan (DHA-PPQ), KyainSeikkyi in Kayin state (CQ) and Kawthaung in Tanintharyi state (AL and CQ). In 2022, Myanmar plans to conduct TES in Tamu in Sagaing state (AL and CQ) and Buthidaung in Rakhine State (AL, DHA-PPQ, CQ, and K13 and partner drug resistant markers analysis).

3.4 Viet Nam

In 2021–2022, Viet Nam will undertake TES for AS-PY in three sites: Binh Phuoc, Dak Lak and Gia Lai. TES will be conducted for DHA-PPQ in Phu Yen and for CQ in Gia Lai. DHA-PPQ will be tested in iDES in Binh Thuan and Kon Tum. In Dak Nong, Pryramax will be tested in iDES.

3.5 China (Yunnan Province)

In 2021–2022, Yunnan Province of China will continue iDES for DHA-PPQ and CQ and include all health facilities in order to scale up the coverage to the whole country for all cases of malaria. In addition, focus will be placed on improving the timeline through the 1-3-7 approach especially from

hospitals to ensure patients are placed on follow-up schedules. In parallel, activities will start for QC for molecular markers and to strengthen laboratories for microscopy QA.

3.6 Thailand

In Thailand, intensified iDES for 2021 will be conducted for AS-PY, CQ+PQ in Sisaket province and Ubon Ratchathani. The iDES will ensure 100% compliance to NTGs, zero stock-outs of drugs, adequate patient support for follow-up, QC of all slides, and integration of laboratory data and results of molecular markers in the online system. Refresher trainings will be conducted for treatment providers.

4. CONCLUSIONS AND RECOMMENDATIONS

Dr James Kelley, Technical Officer, WHO Regional Office for the Western Pacific, thanked the GMS country participants, the donors and partners for their comments and support. He encouraged country programmes and the WHO Secretariat to carefully review the recommendations so that swift action can be taken in accelerating elimination.

4.1 Conclusions

Overview of GMS malaria elimination: From January to September 2020, the GMS countries demonstrated an approximately 61% decrease of *P. falciparum* cases and a 32% decrease of *P. vivax* cases compared to the same period in 2019. Implementation of activities continued as expected despite the COVID-19 pandemic. The relative importance of *P. vivax* cases is likely to increase as countries approach elimination; 82% of cases currently are *P. vivax*. Malaria is mostly concentrated in remote areas, where the disease disproportionately affects travellers to malaria-risk areas as well as mobile and migrant populations. Intensification strategies are being planned and implemented to reach those at highest risk, particularly in Cambodia, which is launching an aggressive approach.

Status of artemisinin resistance: Data suggest that there has been no major increase in artemisinin partial resistance and multidrug resistance in the past year. GMS countries face a critical window of opportunity to eliminate *P. falciparum*.

National treatment guidelines (NTGs): ACTs are available and have been tested for efficacy throughout the GMS. All countries are in the process of changing their second-line treatment to ACTs, in place of quinine. Thailand has adopted AS-PY in two provinces along its border with Cambodia, and Viet Nam has begun using AS-PY in provinces reporting more than 10% failures of DHA-PPQ. Low-dose PQ for the treatment of *P. falciparum* malaria is included in all NTGs but is not fully operationalized in all countries.

Drug efficacy: TES are the gold standard for monitoring drug efficacy to inform treatment policy. In 2020, the COVID-19 pandemic caused delays in activity implementation in some countries resulting in some additional challenges to follow-up.

- **Cambodia:** AS-MQ and AS-PY are demonstrating optimal efficacy. Piperaquine resistance has been detected in Cambodia, leading to policy change.
- **Lao People's Democratic Republic:** Similar to Cambodia, AS-MQ and AS-PY are efficacious. The data on AL between 2019 and 2020 show that AL remains highly efficacious.
- **Myanmar:** Data suggest that AL, AS-PY, DHA-PPQ and CQ (for *P. vivax*) remain highly efficacious.
- **Viet Nam:** National data suggest that AS-PY and AS-MQ are also efficacious, while DHA-PPQ shows lower levels of efficacy in at least four provinces. Molecular data indicate piperaquine resistance in Viet Nam.

- **Thailand:** DHA-PPQ is efficacious at the border with Myanmar, while AS-PY became the first-line treatment in the country's northeast due to high DHA-PPQ resistance. CQ (for *P. vivax*) showed efficacy in 2019 and 2020 compared to 2018 (Sisaket).
- **China (Yunnan):** No TES has been conducted in Yunnan since 2016 due to low malaria incidence. iDES formally started in Yunnan in areas bordering Myanmar in 2020.

Integrated drug efficacy surveillance (iDES): In elimination settings, the collection of drug efficacy data can be shifted from a system comprising sentinel sites to an iDES system. Cambodia, China (Yunnan Province), the Lao People's Democratic Republic, Thailand and Viet Nam have piloted iDES, and Cambodia plans to scale up iDES in all pilot areas in 2021. Starting in 2021, the Lao People's Democratic Republic will be scaling up iDES in 125 elimination districts and incorporating it as a routine component of case investigations. Thailand has expanded iDES nationwide and used data to drive policy change.

Quality control monitoring: Monitoring helps to identify gaps and challenges for improvement in TES and iDES implementation. In the past year, most countries were able to continue QC activities, but travel restrictions due to COVID-19 have caused some delays.

Genetic markers: The efficacy of AS-MQ and resistance to piperaquine are confirmed by molecular markers in Cambodia, the Lao People's Democratic Republic, Thailand and Viet Nam. AS-MQ introduction is clearing KEL1/PLA1 strains (artemisinin and piperaquine resistant) in Cambodia. There is a potential risk of the spread of the triple mutant (piperaquine, mefloquine and artemisinin) associated with the implementation of triple ACTs. AQ-R is confirmed in Cambodia. Close monitoring, therefore, remains crucial for Cambodia.

4.2 Recommendations

4.2.1 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, while ensuring proper front-line workers safety in the context of the COVID-19 pandemic.
2) Continue efforts to strengthen quality assurance 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) NMPs should continue to work with country national regulatory agencies 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 COVID-19, 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 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) 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 AS-PY as regards 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.

4.2.2 Recommendations for WHO

WHO is requested to consider the following:

Regional Office

1) Support countries to review and revise NTGs based on available TES data and other information and coordinate in resolving bottlenecks with NRAs.

MME programme

1) Provide support to GMS countries on TES implementation based on standard guidelines, national workplans and budgets.

2) Support countries moving towards elimination, particularly as they transition to iDES, including finalizing iDES protocols and scaling up activities to ensure drug efficacy in elimination settings.

Country offices

1) Support the operationalization of revised NTGs with partners.

ANNEX 1

Programme agenda

Day 1: Wednesday, 28 October 2020		
Opening Session		
13:00 – 13:30	Welcome address from WHO Representative Cambodia Opening remarks from Global Malaria Program	Dr Li Ailan, WHO Representative Cambodia Dr Pascal Ringwald
	Meeting objectives	Dr Luciano Tuseo, Coordinator, Mekong Malaria Elimination (MME) Programme
	Introduction of country teams and observers	
	Nomination of Chair, Co-Chair and Rapporteur D1 and D2	
	Administrative - virtual meeting rules and announcements	Dr Maria Dorina Bustos, Malaria Technical Officer
	Chairperson for Day 1: Dr Aung Thi, Director, NMP, Myanmar	
Session 1:	Regional updates	
13:30 – 13:45	Review of Recommendations 2019 and Progress	Dr Maria Dorina Bustos
13:45 – 14:15	Overview of the Mekong Malaria Elimination Program in the GMS	Dr Luciano Tuseo, Coordinator, Mekong Malaria Elimination (MME) Programme
14:15 – 14:45	Updates on Global anti-malarial drug resistance, including partial resistance to artemisinin and partner drugs in the Greater Mekong Subregion	Dr Pascal Ringwald, Coordinator, Global Malaria Programme
14:45 – 15:00	Plenary Discussion	
Session 2:	Country Presentations from Greater Mekong Subregion TES (10 min country presentation, followed by discussion)	
15:00–16:00	Cambodia	CNM TES Principal Investigator
	Lao PDR	CMPE TES Principal Investigator
	Myanmar	DMR TES principal Investigator
	Viet Nam	NIMPE TES Principal Investigator
16:00-16:10	*Coffee / tea break*	
Session 3:	Integrated drug efficacy surveillance and QC in TES/iDES implementation	
16:10 – 17:00	Yunnan, China	NIPD Principal Investigator
	Thailand	DVBD Principal Investigator

Day 2: Thursday, 29 October 2020		
	Chairperson for Day 2: Dr Nguyen Quang Thieu, Vice Director of NIMPE	
Session 4:	Updates on antimalarial resistance and molecular markers	
13:00 – 13:30	Different dug efficacy surveillance systems: routine TES, integrated drug efficacy surveillance (iDES) in the context of elimination, and importation	Ms Charlotte Rasmussen
13:30 - 14:00	Quality Control in TES and iDES: implementation challenges	Dr Maria Dorina Bustos
14:00 - 14:30	Updates on Kelch 13, Plasmepsin and other molecular markers for resistance in the GMS – Q&A	Dr Benoit Witkowski Institut Pasteur du Cambodge
14:30 – 14:45	Review of challenges affecting effective management of malaria in the context of current pandemic situation	Dr Neena Valecha, Malaria Regional Adviser, CDS/SEARO
14:45-14:55	Plenary discussions Q&A	
14:55 – 15:00	*Coffee/tea break*	
Session 5:	Planning and budget: TES, integrated Drug Efficacy Surveillance (iDES) and molecular markers	
15:00 – 16:15	• Introduction to country plans • Plenary presentation and discussion of country plans / drug resistance surveillance and budget (10 mins / country); Q & A - Cambodia - Lao People's Democratic Republic - Myanmar - Viet Nam - China (Yunnan) - Thailand	Facilitators: Dr Maria Dorina Bustos/ Charlotte Rasmussen, WHO country staffs • Presenters: Country TES Principal Investigators
16:15 – 16:30	Partners' comments: BMGF, CHAI, GFATM, USAID/PMI, UCSF, UNOPS, RSC-IMP	
Session 7:	Next Steps & closing	
16:30 – 16:45	Conclusion, next steps and recommendations	Dr Pascal Ringwald
16:45 – 17:00	Closing	Dr Luciano Tuseo

ANNEX 2

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