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

28–29 September 2017
Ho Chi Minh City, Viet Nam
MEETING REPORT

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

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NOTE

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

This report has been prepared by the World Health Organization Regional Office for Southeast Asia and the Western Pacific for those who participated in the Fifth Meeting of the Greater Mekong Subregion (GMS) Therapeutic Efficacy Studies (TES) Network held in Ho Chi Minh City, Viet Nam on 28-29 September 2017.
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**Keywords:**

Asia, Southeastern / Drug resistance / Malaria / Regional health planning
# Abbreviations

<table>
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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACPR</td>
<td>Adequate clinical and parasitological response</td>
</tr>
<tr>
<td>ACT</td>
<td>Artemisinin-based combination therapy</td>
</tr>
<tr>
<td>AL</td>
<td>Artether + lumefantrine (Coartem™)</td>
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<tr>
<td>AM</td>
<td>Artether</td>
</tr>
<tr>
<td>AS</td>
<td>Artesunate</td>
</tr>
<tr>
<td>AS-AQ</td>
<td>Artesunate + amodiaquine</td>
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<tr>
<td>AS+SP</td>
<td>Artesunate + sulfadoxine-pyrimethamine</td>
</tr>
<tr>
<td>ASMQ</td>
<td>Artesunate + mefloquine</td>
</tr>
<tr>
<td>AS-PYR</td>
<td>Artesunate + pyronaridine tetraphosphate (Pyramax™)</td>
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<tr>
<td>BVBD</td>
<td>Bureau of Vector Borne Diseases</td>
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<tr>
<td>CNM</td>
<td>National Center for Parasitology, Entomology and Malaria</td>
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<tr>
<td>CQ</td>
<td>Chloroquine</td>
</tr>
<tr>
<td>DHA-PIP</td>
<td>Dihydroartemisinin + piperaquine</td>
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<tr>
<td>ERAR</td>
<td>Emergency Response to Artemisinin Resistance</td>
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<tr>
<td>G6PD</td>
<td>Glucose-6-phosphate dehydrogenase</td>
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<tr>
<td>iDES</td>
<td>Integrated drug efficacy surveillance</td>
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<tr>
<td>IPC</td>
<td>Institut Pasteur du Cambodge</td>
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<tr>
<td>K13</td>
<td>Kelch 13</td>
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<tr>
<td>MQ</td>
<td>Mefloquine</td>
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<tr>
<td>MME</td>
<td>Mekong Malaria Elimination</td>
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<td>NIMPE</td>
<td>National Institute of Malariology, Parasitology and Entomology</td>
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<td>NIMR</td>
<td>National Institute for Malaria Research</td>
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<td>NIRTH</td>
<td>National Institute for Research in Tribal Health</td>
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<td>NMCP</td>
<td>National Malaria Control Programme</td>
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<td>NTG</td>
<td>National Treatment Guidelines</td>
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<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
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<tr>
<td>Pf</td>
<td><em>Plasmodium falciparum</em></td>
</tr>
<tr>
<td>Pfpm2-3</td>
<td>Pf plasmepsin 2-3</td>
</tr>
<tr>
<td>Pm</td>
<td><em>Plasmodium malariae</em></td>
</tr>
<tr>
<td>Po</td>
<td><em>Plasmodium ovale</em></td>
</tr>
<tr>
<td>Pv</td>
<td><em>Plasmodium vivax</em></td>
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<tr>
<td>PMI</td>
<td>President’s Malaria Initiative</td>
</tr>
<tr>
<td>PQ</td>
<td>Primaquine</td>
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<tr>
<td>QA</td>
<td>Quality assurance</td>
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<tr>
<td>QC</td>
<td>Quality control</td>
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<tr>
<td>RDT</td>
<td>Rapid diagnostic test</td>
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<tr>
<td>TES</td>
<td>Therapeutic efficacy studies</td>
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<tr>
<td>USAID</td>
<td>United States Agency for International Development</td>
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<td>WHO</td>
<td>World Health Organization</td>
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SUMMARY

The Fifth Meeting of the Greater Mekong Subregion (GMS) Therapeutic Efficacy Studies (TES) Network was convened in Ho Chi Minh City, Viet Nam on 28-29 September 2017. The meeting brought together participants from the GMS, as well as India. The meeting provided participants with an opportunity to build upon discussions from a 2016 meeting, to review the results and experiences of implementing TES over the previous 12 months, to update national treatment guidelines based on the results generated from TES and to discuss alternative therapeutic efficacy surveillance methodologies for countries moving into elimination.

Delayed response and resistance in falciparum to artemisinin and partner drugs of combination therapies remains a challenge in nearly all GMS countries, with four artemisinin-based combination therapies (ACTs) failing in Cambodia, and increasing evidence of partner drug failures in more provinces of the Lao People's Democratic Republic, Thailand and Viet Nam including confirmed presence of Kelch 13 (K13) mutations and other resistance markers.

The proposed plan for integrated drug efficacy surveillance (iDES) as an alternative option to TES in areas of elimination, wherein an adequate number of cases cannot be enrolled for TES, was presented and discussed. Prerequisites for beginning iDES were clearly outlined. As surveillance is the backbone of elimination, countries planning to move away from TES must have a strong and functioning case-based surveillance system. Integrating drug efficacy monitoring into the surveillance system means that the data collected on malaria cases in the routine surveillance system must also be used to generate information about drug efficacy. There are many countries in the GMS, however, that should continue with TES. For countries that have not yet entered the elimination phase, TES remains the most appropriate option for monitoring drug efficacy and resistance to ACTs.

The objectives of the meeting were:

1) to review and discuss implementation and results of the recent TES in the GMS including related control activities;
2) to discuss the role and results of K13, the molecular marker for tracking artemisinin resistance, and of other molecular markers for monitoring antimalarial drug resistance; and
3) to develop GMS and country work plans and budgets for TES monitoring in 2018-2019.

Conclusions

1) Dramatic reductions in malaria case numbers across the GMS indicate that countries are making progress towards elimination despite reports of increasing resistance in several areas of the subregion. It was noted that in some countries, gaps in universal access to diagnosis and treatment are significant and must be addressed as a priority. All countries reported increasing proportion of Plasmodium vivax infections, with no information on compliance with primaquine (PQ) treatment.

2) Due to the concentration of cases along border provinces in many GMS countries, cross-border collaboration remains important in the GMS, particularly with porous borders and mobile populations. Proper tracking of patients is especially important when analysing data on the origin of cases and whether cases are indigenous or imported. The
implications for ensuring that appropriate treatment is given are significant, given the changes in national treatment guidelines.

3) ACT failures due to resistance to artemisinin and partner drugs remains a challenging issue in GMS countries, with four ACTs failing in Cambodia, and increasing evidence of partner drug failures in more provinces of the Lao People's Democratic Republic, Thailand and Viet Nam with confirmed K13 mutations and plasmepsin 2-3 (marker of piperaquine resistance). In Myanmar, the situation remains stable with partner drugs. Yunnan, China reported zero indigenous cases in 2017, and efficacy of first-line dihydroartemisinin + piperaquine (DHA-PIP) was high among imported cases.

4) Alternative ACTs to current first line treatments such as artesunate + mefloquine (ASMQ) and/or artesunate + pyronaridine tetraphosphate (Pyramax™) are being tested in most countries. In addition, more information on pfmdr1 and plasmepsin 2-3 copy numbers is needed to track resistance to partner drugs in the whole region.

5) The GMS has confirmed artemisinin resistance, so delayed clearance is to be expected for all ACTs, while the same is not true for non-GMS countries (i.e. India). There is an east–west divide. East of Bangkok, partner drugs were not working (ACT failures) and more than 90% C580Y mutations were observed; meanwhile, many patchy K13 markers with partner drugs were working (no ACT failures) west of Bangkok.

6) As countries transition from burden reduction to elimination, it will be important to look at whole-of-system responses and to move from TES to iDES. Strengthening malaria surveillance in elimination settings including case-based surveillance will be important to ensure that each and every case is completely cured and parasite free. This is the desired end-point of iDES, which is fundamentally different from the purpose of the current TES. Thus, having a functional case-based surveillance system and a low enough number of cases to make full follow-up of all cases possible will be essential prerequisites to roll out iDES. Thailand has commenced piloting iDES and plans to scale it up in 2018.

7) Low-dose primaquine (PQ) for falciparum is not implemented in some countries, although all countries have included it in their National Treatment Guidelines (NTG). Administration of low-dose PQ in all confirmed falciparum cases is a priority to minimize the potential spread of resistant falciparum strains in the GMS.

8) Artemisinin monotherapies are still reported to be available in some countries and this remains a serious problem, as does the issue of substandard drugs. In addition, procuring adequate supplies of drugs (such as ASMQ) has become challenging when case numbers are low, as pharmaceutical companies either stop production or refuse to produce small amounts of a given drug. A potential solution to this issue is to explore the possibility of creating a regional virtual stockpile of antimalarials.

Recommendations for Member States

1) Countries are encouraged to continue their efforts in strengthening implementation of high-quality TES using the standard WHO protocol.

2) Countries should continue to strengthen laboratory capacities, particularly microscopy QA, both for current TES and for moving forward to pre-elimination and elimination; and to implement quality control for molecular assays in collaboration with the regional reference laboratory at Institut Pasteur du Cambodge.

3) Alternative ACT regimens need to be tested before declining efficacy becomes apparent.
4) Countries are encouraged to closely monitor TES implementation in the sentinel sites using the WHO monitoring checklist.
5) As countries move towards elimination, a strong surveillance system needs to be in place to facilitate integration of drug efficacy monitoring into routine surveillance.

**Recommendations for WHO**

1) WHO will continue to provide technical assistance in TES and iDES implementation, to share information on artemisinin resistance in the GMS and to provide guidance on national and regional drug policy reviews.

2) WHO will revive the discussion about a regional drug stockpile at the next Regional Steering Committee meeting. A regional drug stockpile would be a potential solution to stock-outs and encourage drug companies to continue to produce greater quantities of these relevant drugs.

3) WHO is requested to continue providing support for countries moving into elimination settings, particularly as they transition to iDES.

4) WHO may continue to explore the idea of rotating first-line drugs. This would require strong supply chain management within countries.

5) Therapeutic efficacy surveillance for ACTs already being used in countries as part of NTG will no longer require ethical clearance as this will be considered as a part of overall malaria surveillance.
1. INTRODUCTION

1.1 Background

The Fifth Meeting of the Greater Mekong Subregion (GMS) Therapeutic Efficacy Studies (TES) Network was convened in Ho Chi Minh City, Viet Nam on 28-29 September 2017. Monitoring antimalarial drug resistance is an important activity of the national malaria programmes as it ensures that malaria treatment policies being implemented are evidence-based, and that early deterioration in the efficacy of recommended treatment regimens is identified in a timely fashion and drug policy recommendations are updated.

In the GMS, there has been an emergence of multidrug-resistant malaria parasites, including some that are resistant to artemisinin-based combination therapies (ACTs), the most potent weapon in treating falciparum malaria. The evolution of artemisinin resistance prompted the development of the Strategy for Malaria Elimination in the Greater Mekong Subregion (2015–2030), which was launched during a side event of the World Health Assembly in May 2015. One of the key components of the new strategy is to intensify surveillance for antimalarial drug resistance in near-elimination settings. All countries and their partners support systematic drug efficacy monitoring using standardized WHO methodologies.

1.2 Objectives

The objectives of the meeting were:

1) to review and discuss implementation and results of the recent TES in the GMS;
2) 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
3) to develop GMS and country work plans and budgets for TES monitoring in 2018-2019.

2. PROCEEDINGS

2.1 Opening session

Dr Rabindra Abeyasinghe, Coordinator, Malaria, other Vectorborne and Parasitic Diseases, WHO Regional Office for the Western Pacific, delivered the opening address on behalf of the WHO Regional Director Dr Shin-Young-soo. Elimination of malaria in the GMS is the key to elimination of malaria in Asia and the Pacific. Significant progress has been made in preventing the spread of artemisinin resistance beyond the GMS, but challenges remain. Efforts must be redoubled to detect resistance to artemisinin and partner drugs as soon as it becomes apparent. Robust surveillance and full access to diagnosis and treatment is the key to eliminating malaria in the region, as is effective coordination across the public and private sectors. Coordination among donors is also critical to ensure that the resources are effectively targeted and allocated within the appropriate time frame for a rapid response.

Professor Le Thanh Dong, Director of the Institute of Parasitology and Entomology in Ho Chi Minh City, welcomed all participants from national programmes, academia, partner institutions and WHO on behalf of the Ministry of Health and the National Malaria Control Programme (NMCP). He noted that one of the key components of the new Strategy for
Malaria Elimination in the Greater Mekong Subregion (2015–2030) is to intensify surveillance for antimalarial drug resistance. The meeting therefore provided a timely opportunity for representatives and principal investigators from NMCPs in the six GMS countries (as well as technical experts and partners) to move the discussion forward through sharing of information and experiences, and to review results and plan the network activities for the next year.

The participants unanimously elected the following officials for the meeting: Dr Huyn Hong Quang of Viet Nam as Chairperson; and Dr Leang Rithea of Cambodia as Rapporteur.

Dr Abeyasinghe noted that there was no conflict of interest (COI) among the participants and temporary advisers as per the completed COI forms submitted to the Secretariat.

The meeting agenda is included in Annex 2, and the list of participants in Annex 3.

2.2 Review of recommendations from 2016 and progress - Dr Dorina Bustos

Recommendations from the Second Biregional Meeting of Asia–Pacific Malaria Drug Resistance Monitoring Networks, held in 2016, encouraged all countries to continue to strengthen high-quality implementation of TES according to the standard WHO protocol; to strengthen quality assurance (QA) by supporting laboratory capacities; to ensure frequent refresher training for TES microscopists; and to implement quality control (QC) for molecular assays with Institut Pasteur du Cambodge (IPC) providing technical training and exchange of samples. Testing alternative ACT regimens as soon as declining efficacy becomes apparent is particularly important in the GMS where artemisinin resistance remains challenging. Facilitating the integration of monitoring of drug efficacy into routine surveillance systems in near-elimination settings was also recommended.

In 2017, countries enhanced quality TES and, in the case of Thailand, piloted implementation of integrated drug efficacy surveillance (iDES). Regular in-country monitoring by NMCP principal investigators and WHO country offices continued for all studies in Cambodia, China (Yunnan), the Lao People’s Democratic Republic, Myanmar, Thailand and Viet Nam. Microscopy capacity was also strengthened across countries through external quality assessments (EQAs) of national malaria laboratories and the establishment and maintenance of slide banks. Alternative ACTs being tested in 2017 include: artesunate + pyronaridine (AS-PYR, Pyramax™) in Cambodia, Myanmar and Viet Nam, and possibly in Thailand following national ERC approval; and dihydroartemisinin + piperaquine (DHA-PIP) in the Lao People’s Democratic Republic. Integrating the monitoring of drug efficacy into routine surveillance systems is being piloted in Thailand in 2017 and in China since 2016.

Dr Abeyasinghe noted that a key recommendation from the 2016 meeting was for countries to improve the quality of diagnostics. Although this issue remains challenging, particularly with reduced numbers of malaria cases, countries need 1) to ensure that their QA systems are strong, functioning and optimally aligned with WHO standards, and 2) to increase awareness of transmission dynamics in sentinel sites so that TES can be implemented when transmission is at its highest.

Dr Christophel noted that good examples of national laboratory plans that institutionalize quality assurance are available and should be shared so other countries can benefit from them. As the region moves towards elimination, countries must document diagnostics QA including a designated national reference laboratory that documents microscopy competence, as this remains the gold standard for diagnosis even where case numbers are declining.
2.3 Strengthening coordination and partnerships to accelerate elimination in the GMS - Dr Hiromasa Okayasu

Dr Okayasu presented on the transition from the Emergency Response to Artemisinin Resistance (ERAR) initiative to the current Mekong Malaria Elimination (MME) programme. Coordination is a key focus of MME and will be achieved through the following activities: partnership forum, advocacy and external communications and a regional surveillance data platform. The GMS Strategy for Malaria Elimination by 2030, was also highlighted. While the epidemiology of malaria in the region points to a significant decline in the numbers of reported cases and deaths in all GMS countries, there are still a number of programmatic, case management, vector control and surveillance issues that need to be addressed and improved, such as cross-border collaboration. Finally, examples of innovation were presented, from diagnostics to digitalized reporting to improve efficiencies.

2.4 Antimalarial drug resistance monitoring in the GMS: progress and implementation challenges: QC monitoring - Dr Dorina Bustos

The WHO in vivo protocol for the assessment of therapeutic efficacy remains the standard guide to monitor drug efficacy to update drug policy. TES sites increased from 32 sentinel sites in 2008 to 51 sites by 2016: Cambodia has 11 sentinel sites; the Lao People’s Democratic Republic, 6; Myanmar, 11; Thailand, 13; Viet Nam, 6; and Yunnan, China, 4. Every six months, the WHO Global Malaria Programme releases an update on artemisinin and ACT resistance with a specific focus on the latest validated TES results and genotypes for molecular markers. In the GMS, ACT failure rates increased between 2016 and 2017. In 2016, China, Myanmar and Viet Nam experienced failure of only one ACT; however, by 2017, Viet Nam joined the Lao People’s Democratic Republic and Thailand with ACTs failing, and Cambodia had four ACTs failing.

Beyond TES, as countries move into near-elimination settings, they need to ensure that as part of their case management, there is a functional microscopy QA system and routine assessments of efficacy of the country’s first-line antimalarial drugs, to detect early evolving signs of drug resistance. This means having the following in place: routine monitoring of therapeutic efficacy as part of surveillance; monitoring of all malaria cases regardless of parasitaemia, age or severity of malaria; supervised treatment; patient follow-up for 28 or 42 days (end point); a team able to follow up patients with case investigation of all malaria cases; and molecular markers as additional tools. Data generated from case-based drug resistance surveillance should be integrated in the programme’s routine surveillance.

Countries were encouraged to review WHO’s Framework for Malaria Elimination, published in 2017, specifically sections on: enhancing and optimizing case detection and case management (2.4); role of QA and national reference laboratories in malaria elimination (2.5); surveillance (2.67); and monitoring drug efficacy, with reference to quality case management and surveillance (2.6.7).

Challenges of monitoring the therapeutic efficacy of antimalarials

Countries across the GMS still experience a number of challenges around TES preparation and implementation. Common concerns include: site selection; protocol review/approval by national and WHO ethics committees; administrative delays in release of funds which culminate in missed peak transmission seasons; failure to adhere to study protocols; inadequate documentation and reporting systems; missed information and challenges of supervised treatment (in P. vivax TES, compliance with 14-day primaquine [PQ] therapy); and quality of slides in some countries. Genotyping of malaria parasites (msp1, msp2 and glurp) is being done sequentially and needs to be done together to differentiate recrudescence
from reinfection. Quality control and validation of study data were also highlighted as ongoing challenges.

The QC monitoring procedures were reviewed. The QC checklist was designed to assist countries to improve TES implementation and monitor sites on a monthly basis. Both the Lao People’s Democratic Republic and Myanmar noted the value of the checklist, particularly in identifying discrepancies at the point of care and providing opportunities to discuss solutions with investigators. The QC checklist should be included in all TES reports. However, some noted that the checklist is too detailed and could be refined. A representative from the United States Agency for International Development (USAID) commented that while QC had been an issue, as there had been limited information as to whether protocols were being followed. The purpose of the checklist was to identify bottlenecks and then fix them. The checklist was meant to improve TES implementation.

Integrated drug efficacy surveillance (iDES) is designed to include all malaria cases, whether imported or indigenous. Country-level protocols for iDES are still under development. Thailand has developed and is piloting its own protocol. China still requires national direction on implementation.

2.5 Presentations by principal investigators on TES results

Cambodia - Dr Leang Rithea

A summary of malaria trends from 2000 to 2015 showed a steady decline in malaria deaths since 2009. Resistance to artemisinin-based combination drugs has been an ongoing challenge for Cambodia, though the country has made admirable progress in testing alternative ACTs. Results from the 2015 TES indicate that DHA-PIP resistance has spread to the north and eastern parts of Cambodia. With the widespread DHA-PIP treatment failures, artesunate + mefloquine (ASMQ) completely replaced DHA-PIP nationwide from 2016 onwards.

Dr Ringwald congratulated Cambodia for its excellent progress in combating malaria. Regarding the testing of alternative ACTs, he cited the successful introduction of low-dose PQ during TES, and expressed his hope that the National Center for Parasitology, Entomology and Malaria Control (CNM) would introduce it nationwide. WHO views low-dose PQ as safe and effective. This is also a good example of the value of TES in integrating research data into policy change. Regarding the number of ACTs failing in Cambodia, WHO is currently reviewing all studies of failures to artemether + lumefantrine (AL) since 2010. Since AL has shown an efficacy of 95% since 2012, WHO will revise the situation in Cambodia to show failures of only four ACTs.

In the GMS, delayed clearance of parasitaemia should not be a cause for alarm since we know that artemisinin resistance is already present in the region. Rather than focusing on delayed clearance, countries should look at the partner drug and treatment failures. One exception however was India, where delayed clearance would indeed signify a possible problem.

Dr Abeyasinghe reiterated that WHO would like to receive reports of national transmission patterns on a monthly basis, especially at sentinel sites, to ensure that transmission season is not missed. In addition, WHO would like to know how much on-site supervision is happening by principal investigators. Use of transmission data to generate good TES data based on adequate sample size, will contribute to understanding sensitivity patterns and providing efficacious treatment and will ultimately lead to elimination. Transmission data are needed to plan better and to ensure that TES start on time, since it is important to link TES to routine surveillance. Understanding the seasonal transmission and geographical distribution of burden will also help in site selection and determine where resources should be invested.
Dr Ringwald explained that resistance to piperaquine could emerge and spread very quickly. The current state of artemisinin resistance could be a factor as well as massive use of DHA-PIP, which is not good for the region. Dr Abeyasinghe added that since the goal is to eliminate the spread of resistant parasites, then rapid implementation of low dose PQ in Cambodia and the Lao People’s Democratic Republic is necessary and is preferably given on Day 0. Cambodia confirmed that low dose PQ has been integrated into the National Treatment Guidelines (NTG) already and the drug is being distributed throughout the system.

Lao People’s Democratic Republic - Dr Keobouphaphone Chindavongsa

Following the outbreak of 2011, the proportion of falciparum cases has declined while the proportion of vivax infections have gradually increased, accounting for nearly 61% of all cases in 2016. During the year, DHA-PIP for *Plasmodium falciparum* (Pf) was tested in military and civilian populations in Champasack Province, and AL was tested in Salavanh Province. Preliminary results show both drugs to be failing with ACPR rates as follows: DHA-PIP (civilian), 39.1%; DHA-PIP (military), 60%; and AL, 60%. Final results should be available by the end of 2017. The NTG are due for review by the end of 2017 because of the decreasing efficacy of AL and DHA-PIP in treating Pf malaria. Primaquine needs to be rolled out to address the increasing proportion of vivax malaria.

WHO expressed serious concern about the failure of DHA-PIP in the Lao People’s Democratic Republic. Since the drug has never been used in the country, its failure indicates the presence of DHA-PIP resistance. A hypothesis is that DHA-PIP drugs may be circulating in the country – either legally or illegally. The drug is being used across the country’s borders in Cambodia, Thailand and Viet Nam. Piperaquine has long been used as a monotherapy and may still be used in the private sector. An ACTwatch survey (including a monotherapy watch) was proposed to assess available drugs in pharmacies and private sector facilities.

The issue of mobile populations and the military was discussed. As parasites can be easily carried across borders, more information from mobile patients is required. TES conducted close to borders provide a snapshot only of the mobile population. Therefore, caution is warranted in terms of interpreting these data, as there are no trends over time. In Sisaket, Thailand, the same issue is evident and questions arise whether there is spread of DHA-PIP-resistant parasites. This will be discussed further in the international forum of the civil/military meeting to gain a clearer picture of what other drugs the military are using.

Myanmar - Dr Aung Thi

Despite Myanmar’s success in combatting malaria, 291 of the country’s 330 townships are still malaria-endemic with approximately 43.9 million people at risk. In 2016, 110 146 cases and 21 deaths were reported. Children under 15 years of age accounted for almost 70% of all cases between 2010 and 2016, and Pf accounted for 60% of cases. Malaria deaths have declined steadily since 2001.

Artemisinin resistance is not evident in Myanmar. All partner drugs are working, providing an important buffer zone to prevent resistance spreading to Bangladesh and India. It will be important to continue monitoring resistance in order to have updated information so that the country can update the treatment regimen accordingly. In 2016, TES conducted in several sites showed: in Buthidaung (Rakhine), an adequate clinical and parasitological response (ACPR) of 98.2% for AL, 98% for DHA-PIP, and 98.2% for chloroquine (CQ) with D3 positivity rate of 1.6%; in Tamu (Sagaing), an ACPR of 98.1% for AL with D3 positivity of 1.9%, and 100% for DHA-PIP and CQ; and in Tabeik-kyin (Mandalay), an ACPR of 96.2% for AL with D3 positivity of 3.7%, and 100% for DHA-PIP and CQ. TES are ongoing in Mon and Kayin states; in MyintKyiNar (Kachin) and Kyaut-Me (Shan), testing AL and AS-PYR;
and in Kyar Inn Seik Kyi (Kayin) and Mawthaung and Kawthaung (Thanintharyi), testing AS-PYR and CQ.

The prevalence of Kelch 13 (K13) mutations shows the emergence of mutations in different areas except along the western border. The K13 mutant rate is 21%; however, co-prevalence of K13 and other markers is not very high, reflecting low partner drug resistance. Other molecular markers should therefore be used for early detection of multidrug-resistant falciparum malaria in Myanmar.

Dr Ringwald commented that 17 years into artemisinin resistance, it appears that the GMS can be divided into two subregions – east and west of Bangkok. East of Bangkok, one specific K13 molecular marker, C580Y, is prevalent in Cambodia and the Lao People’s Democratic Republic, sometimes almost 100% in Cambodia. On top of this, many partner drugs are failing. West of Bangkok, the situation is patchy with many K13 markers – not one – taking over. At the China–Myanmar border, despite the presence of F446I, the partner drugs are all working. Myanmar confirmed that there is no plan to change treatment of CQ for vivax as evidence-based data are being followed. A TES is planned for 2017 with vivax and CQ. Dr Ringwald reiterated the importance of ensuring the efficacy of CQ for vivax as studies in 2009 (20%) and 2012 (30%) showed high treatment failures in Kawthaung. However in 2014, the treatment failures were reduced again to 2%.

Thailand - Mr Theerayot Kobasa

Thailand’s case numbers have continued to decline with a 16.5% reduction between 2016 and 2017. *P. vivax* (Pv) and Pf accounted for more than 77% and 15%, respectively, of all malaria cases between 2000 and 2017. Malaria transmission occurred in only 43 provinces during 2016, with the population at risk reduced from 1.3 million to 1.0 million. The number of forest-goers in at-risk provinces also came down, though they accounted for 17% of the at-risk population in both years. Thai NTG specify DHA-PIP as the first-line treatment for uncomplicated falciparum malaria. TES conducted from 2010 to 2016 revealed the following: in 2012, ACPR of 75% for ASMQ in Kanchanaburi and 88% in Ubon Ratchathani; in 2014, ACPR of 80% in Tak and D3 positivity of 30% in Ratchaburi; and in 2016, ACPR of 100% for ASMQ in Srisaket, Songhkla, Yala and Surathani.

Molecular marker results in 2016 showed the following: out of 277 Pf cases confirmed by polymerase chain reaction (PCR), 156 (56%) isolates had K13 mutation, of which 123 (44.4% of total) isolates had confirmed artemisinin-resistant mutation. Preliminary findings from 2017 survey samples indicate that 24.82% of isolates had K13 mutation, which correlated with delayed parasite clearance. In addition, 29.01% had a Pf Kelch 13 correlating with delayed parasite clearance and treatment failure. An analysis of K13 mutations between 2007 and 2016 showed an increasing proportion of C580Y and R539T mutations (ranging from 25% to 90%) mainly along the eastern Thai-Cambodia border in the provinces of Srisaket, Ubon Ratchathani, Trat and Chanthaburi. C580Y is the predominant mutation along the western Thai-Myanmar border in the provinces of Tak, Kanchanaburi and Ranong.

Viet Nam - Dr Bui Quang Phuc

A comparison of data from 2006 to 2016 showed the number of cases had declined by 81.6% and deaths had been reduced by 92.7%. *P. falciparum* malaria accounted for 79% of all cases in 2006 but only 56% by 2015, with a proportionate increase in the percentage of *P. vivax* cases (42% by 2016). The 2016 NTG stipulate that first-line treatment is DHA-PIP (Arterakine™ or CV-Artecan™), second-line treatments for *P. falciparum* are Quinine plus doxycycline (7 days) and Quinine plus clindamycin (7 days); and alternative ACTs are AS-AQ, AL and AS-PYR.
TES activities in 2016 carried out in four provinces showed ACPR of 100% in Dak Lak, 96.4% in Khanh Hoa, 53.7% in Binh Phuoc, and 73% in Dak Nong against tested antimalarials. The proportion of D3 positives is high, ranging from 10.8% to 46.3% in all provinces. Together with the high proportion of D3 positives, K13 propeller mutations such as C580Y and I493H confirmed AS resistance in several sentinel sites in Viet Nam. Preliminary results from an ongoing 2017 TES with AS-PYR (Pyramax™) indicated that AS-PYR is highly efficacious for *P. falciparum* malaria in known resistant areas.

With the increasing trend of DHA-PIP resistance, there are issues of drug registration and regional procurement of drugs for alternative ACTs. Drug manufacturers refuse to produce these drugs because of the small quantities requested. A regionally coordinated procurement could resolve this by ensuring a high enough demand for drugs that would encourage the companies to produce. Dr Ringwald cautioned that resistance to DHA-PIP could spread extremely quickly in Viet Nam, as in Cambodia, and therefore this issue needs to be considered from a subregional perspective. He encouraged Cambodia and Viet Nam to continue with AS-PYR studies and recommended in early 2018 an urgent policy meeting between Cambodia, the Lao People’s Democratic Republic and Viet Nam to address this regional problem.

Binh Phuoc is in close proximity to the Cambodian border. That could mean that many patients were infected while working on the other side of the border. Hence, it is important to determine how much is indigenous infection. Another question to consider is whether changing the NTG was prudent for just two provinces. One approach is to look at samples from Viet Nam. Even without doing an ASMQ study, the ongoing AS-PYR study will give background molecular information on Pf plasmepsin 2-3 (Pfpm2-3) and the pfmdr1 copy number assays that can speed up decision-making. It is very encouraging to see 62 cases enrolled in five provinces, but a minimum of 50 cases will be needed in each province to be sure about AS-PYR efficacy. Viet Nam would need to implement changes proposed to the NTG in September 2016 in provinces with the highest resistance, without further delay because of unavailability of drugs.

### 2.6 Integrated drug efficacy surveillance

**Yunnan, China - Dr Fang Huang**

From 2006 to 2016, China’s malaria caseload declined from 64,178 to three (03) indigenous cases, respectively, with a reported 3140 imported cases in 2016. There were no deaths due to malaria among locally acquired cases in 2016. Twenty-four provinces reported mostly imported malaria cases, with the six provinces with the highest number located in eastern and south-western provinces, especially along the China-Myanmar border. Only three counties in two provinces reported local transmission in 2016. The current NTG specify the following: for *P. falciparum*, - ACTs or pyronaridine + PQ or ACTs (DHA-PIP, AS-AQ and AS-PIP); for *P. vivax*, *P. ovale* and *P. malariae*, CQ + PQ (8 days) or piperaquine/pyronaridine/ACTs for CQ treatment failure; and for severe malaria, intravenous AS, artemether (AM) or pyronaridine.

TES in 2016-2017 showed 100% efficacy of DHA-PIP (Pf) and of CQ (Pv) in Yingjiang on 17 imported cases. Conducting TES on indigenous patients has been difficult because of very low case numbers. As a result, China has commenced piloting of iDES focusing on imported cases. In order to continue integrated drug monitoring, more training and technical support is needed, particularly on the integrated drug monitoring protocol, microscopy QA and national slide bank and external monitoring from WHO. Overall, the efficacy of ACTs is stable with no confirmed artemisinin resistance observed along the China-Myanmar border. The prevalence of the K13 F446I mutation is high, and this mutation is associated with an
intermediate rate of delayed clearance. Lack of the amplification on plasmepsin 2 from parasites with or without K13 mutations indicated no piperaquine resistance emergence along the China-Myanmar border.

Since TES studies started in 2009, China initially used artesunate monotherapy with high D3 positivity. Recent data show high efficacy of DHA-PIP on the border with Myanmar. Myanmar is also reporting high efficacy, which is reassuring. Regarding vivax malaria, Dr Abeyasinghe noted that while the current regime of PQ for 8 days works for Chinese vivax strains, it might be important to move to a 14-day regime for imported cases. The presence in China of the piperaquine monotherapy and possible use of piperaquine monotherapy in the private sector of other GMS countries may explain why PIP is failing in GMS countries.

Thailand

Thailand moved from TES to iDES because of the low number of malaria cases in some provinces. A pilot iDES commenced in May 2017 in three provinces of northern Thailand: Chiang Mai, Chiang Rai and Mae Hong Son. All health facilities are included: malaria posts, border malaria posts, malaria clinics, health-promoting hospitals and hospitals (public and private hospital). An iDES reporting form adapted from the in vivo form includes patient history, history of diagnosis and treatment, follow-up information on parasite count/white blood cell count, body temperature, gametocyte, side effects and a sample collection checklist (blood slide, dried blood spot [DBS] and drug envelope). An online surveillance system is in place.

The goal of implementing iDES in Thailand is to accelerate malaria elimination. Developing appropriate innovative measures and models, establishing national and international collaboration, and promoting community capacity-building will help achieve this. Key activities will include implementing real-time notification/investigation/response (1-3-7 strategy); improving diagnosis and treatment at all health stations; intensifying active case detection; increasing ITN coverage; ensuring compliance to treatment and follow-up, and integrating iDES into routine surveillance.

As iDES is a pilot project, there will be an opportunity to see gaps in slide quality and address them. Regarding the effectiveness of family and community for treatment adherence, Thailand uses self-reporting and supervised treatment. Knowledge, attitude and practices (KAP) and malaria surveys are implemented every two years, and 90% of patients complete them. WHO will finalize the iDES protocol before countries scale up surveillance.

Dr Christophel noted the many cases in the south and along the Myanmar border in 2017, and queried the obstacles to TES in these areas. Thailand responded that of the 3000 cases in Tak, only 900 were Thai and the rest were Myanmar nationals who crossed the border daily for treatment at refugee camps. Tak province will conduct the AS-PYR TES next year. Performing TES in the south is very difficult since it is a conflict zone. It was noted that case numbers dropped by 50% from early 2017 to the present. Community involvement in malaria elimination will be increased with the use of local religious organizations and health volunteers to implement treatment and follow-up.

2.7 Integrating drug efficacy surveillance into routine surveillance system in areas pursuing malaria elimination - Dr Pascal Ringwald

Dr Ringwald explained the difference between the regular TES and iDES. In areas with moderate transmission, TES remains the gold standard for monitoring drug efficacy to inform treatment policy change for both Pf and Pv, and for any drug that needs to be tested prior to possible introduction into the treatment policy. TES is carried out in sentinel sites, with a view to testing the therapeutic efficacy of a drug through monitoring the response of a
number of patients to ensure a minimum sample size is reached. However, in very low transmission areas pursuing malaria elimination, the number of malaria cases is most often too low for the needed number of cases making up the required sample size to be reached in a given sentinel site. Thus in near-elimination areas with strengthened surveillance systems, iDES can be used to follow up all positive cases detected to determine the response to a particular drug. iDES envisages follow-up of all patients in elimination settings to monitor for parasite clearance, relying largely on data collected via routine strengthened case-based surveillance systems.

It was explained that integrating drug efficacy monitoring into the surveillance system is not a simplified TES, that is, a sentinel surveillance system with data only being collected in a selected number of sentinel sites per country, province or district. Integrating drug efficacy monitoring into the surveillance system is ensuring that the data collected on all malaria cases in the routine surveillance system can and are used to generate information about drug efficacy. Countries with elimination-level malaria transmission wanting to move from TES to iDES must ensure they have a strong and functioning surveillance system, that is: a system able to report whether these cases are detected in the public or private system (malaria often becoming a notifiable disease) through passive, active and reactive case detection; a system for providing all cases with supervised treatment; a system for patient follow-up done by the public sector (health centres, hospitals, mobile teams, etc.), private health sector and community services (VHW, MHW) and finally a system to collate, compile and analyse the data by NMCP. The shift to relying on data from routine systems typically only happens when there are very few cases, and when the resources are available to allow for full monitoring of such remaining cases.

Mandatory activities for iDES include: 1) patient classification (imported, indigenous, etc.), with a case investigation and recording of likely origin of the malaria; 2) diagnosis on day 0 using symptoms and species identification by rapid diagnostic test (RDT) and/or microscopy; 3) microscopy diagnosis on final day of follow-up; 4) glucose-6-phosphate dehydrogenase (G6PD) test for vivax patients; 5) supervised treatment including PQ for vivax patients; 6) in case of treatment failures, supervised second-line treatment and follow-up for an additional full follow-up period; 7) for Pf, end-date follow-up period at day 28 or day 42 depending on half-life of drugs given for treatment, and for Pv, end-date follow-up at day 28 and 6 months (for relapse); 8) end-date defined as final day of the follow-up period with cure (see above), or any day the patient presents with recurrent parasitaemia after a treatment (additional full follow-up period is needed with new treatment); and 9) during the follow-up days, clinical symptoms, temperature, and parasitaemia at day 0, end-day or any day of recurrent parasitaemia are all recorded.

Other recommended activities include blood collected at day 0 and day of failure for analysis of markers of reinfection or recrudescence, for analysis of markers of drug resistance, for PCR diagnosis (optional), for genetic analysis to better facilitate identification of geographic origin of parasites; additional follow-up on day 3, and then weekly follow-up on days 7, 14, 21, 28, 35, 42, (49, 56) for Pf and days 7, 14, 21, 28 and on a monthly basis until 6 months for Pv.

Asymptomatic cases can also be included in monitoring. Any patient carrying a single species of parasite (mono infection) must be included in iDES. In the case of confirmed G6PD deficiency, an 8-week treatment of weekly PQ instead of 14 days is recommended. Follow-up and observation for relapses is essential and must be treated accordingly. The end point of iDES should be that all cases are confirmed cured and cleared of parasitaemia, as confirmed by microscopy. Ensuring and sustaining microscopy QA in elimination settings remains a big challenge.
It was questioned how the model of Thailand could be applied to countries with low case numbers and a weak surveillance system. Dr Ringwald responded that if iDES cannot be done as per given prerequisites, then the country is not ready to move to elimination. In Viet Nam, there are many TES studies in progress, but priorities need to be set and TES can still be conducted in well-defined settings. There will also have to be some reliance on molecular markers. Surveillance and microscopy are the backbone of elimination, as referred to in the WHO 2017 Framework for Malaria Elimination.

Dr Abeyasinghe questioned why Viet Nam was not able to recruit sufficient numbers of patients for TES at some sentinel sites and whether the correct sites were identified for the purpose. In some contexts, TES were conducted in zones where case numbers were still high in many hard-to-reach areas. In terms of maintaining quality microscopy, microscopy networks need to move towards a “centre of excellence” model. Gaps in surveillance systems and microscopy QA have to be addressed as a priority, particularly in elimination settings where malaria-specific funding is limited.

Dr Sintasath sought clarification on the statement that iDES is not meant for drug policy change. He explained that in the GMS, there are myriad issues with drug resistance, and asked how a country such as Thailand, for example, would know when it is time to change drugs. He acknowledged the need to monitor regularly but questioned whether, in addition, there could be a process or an indicator to assist in the decision to change drug policy. Dr Ringwald explained that one to two treatment failures may be expected, but if there were more, then the data need to be carefully analysed. If high recrudescence were evident, this would require discussion and need a foci investigation. Continuous high-quality monitoring will indicate the possible presence of treatment failures that can then be resolved appropriately.

2.8 Country presentation from South-East Asia Region

India - Dr Praveen K. Bharti and Dr Kuldeep Singh

The malaria burden in India is disproportionate in the tribal states, with Odisha in the east contributing some 28% of cases, despite having only 2.4% of the population. Jharkhand with 2.9% of the population contributes 13% of all cases, followed by Chhattisgarh with 11% of cases. In total, 91 districts (about 5% of the country’s total population and 31% of total population) contribute 44% of India’s total malaria cases. Of these cases, 68% are Pf. These districts also account for 43% of malaria deaths. Cases rose again in 2015 and 2016.

The current treatment regimen for uncomplicated *P. falciparum* malaria is as follows: in north-eastern states, AL+PQ; and in the rest of India, AS+SP + PQ on D2. For *P. vivax* malaria, the treatment is CQ (3 days) + PQ (14 days); mixed, ACT + PQ (14 days). The treatment for severe malaria is initial parenteral treatment for at least 48 hours: quinine followed by oral doxycycline or clindamycin; intravenous or intramuscular AS; intramuscular AM; or intramuscular artemether followed by ACT.

Evidence from monitoring drug resistance helped to inform drug policy changes such as replacement of AS+SP with AL in north-eastern states and the phase-out of artemisinin monotherapy for uncomplicated malaria. There is still a need to undertake systematic mapping studies to ascertain the role of K13 mutations in artemisinin resistance in the north-eastern region: F4461 in Arunachal Pradesh and A578S and K189T in Mizoram and Tripura. A TES activity (2014–2016) to measure the efficacy of AL and AS+SP in uncomplicated falciparum malaria showed 100 APCR in Jhabua, Anuppur and Simdega, and 92.5% in Baster, and similarly for AS+SP. There is no functional mutation in the K13 gene and limited non-synonymous mutation at codon M579T. Detailed phenotyping and genotyping studies are required for determining the role of K13 in artemisinin resistance. Another TES with AL
started in mid-2017 in four tribal dominated states, namely, Madhya Pradesh, Maharashtra, Chhattisgarh and Odisha.

Regarding AS+SP, India confirmed that there is a local producer of this drug. Dr Christophel sought clarification on the data on molecular markers for SP outside the northern states. Some states like Orissa have double and triple mutations but no quadruple mutations so far.

2.9 Summary of results from GMS countries and India - Dr Eva Christophel

Dr Christophel provided a summary of all country results as well as general conclusions across the GMS.

She noted that four ACTS were failing in Cambodia, with a rapid reduction in DHA-PIP efficacy from 2011 to 2016. ASMQ is effective in all sites with DHA-PIP failures; hence the NTG have shifted to ASMQ across the country. An alternative AS-PYR study is under way. TES has also shown that low dose PQ for Pf is safe in Cambodia.

In the Lao People’s Democratic Republic, AL was efficacious over many years, but failures since 2014 in the south warranted testing DHA-PIP in Champassak, where preliminary results are not good (ACPR <65%), confirmed by the presence of C580Y mutations. This raises questions about whether enrolled patients have acquired infection in countries with DHA-PIP resistance (Champassak borders Cambodia) and if there is high drug pressure in the border areas of southern Lao People’s Democratic Republic.

With more provinces in southern and central Viet Nam showing increasing resistance to DHA-PIP, confirmed with high levels of C589Y mutations and plasmepsin 2-3 markers, results from an ongoing AS-PYR TES are encouraging. A regional meeting on addressing challenges relating to making available effective treatments within NTG is planned for Cambodia, the Lao People’s Democratic Republic and Viet Nam.

Thailand is faced with more than 50% cases in the south, and the rest on the Thai-Myanmar and Thai-Cambodia borders, with 78% vivax cases. The NTG have recommended DHA-PIP since 2015. The K13 mutations vary in areas west of Bangkok, while C508Y seems fixed east of Bangkok, with many partner drugs failing. AS-PYR TES will be tested in Tak province in 2018. Thailand is piloting iDES, but there are still challenges on microscopy QA, human resources for patient follow-up and the need for real-time monitoring for iDES.

In Myanmar, the efficacy of all ACTs remains stable. K13 is present only in south Myanmar, and there is a patchy distribution of different K13 markers in the rest of the country. All partner drugs are working. There are reports of CQ resistance in *P. vivax* in Kawthaung, and they need to be validated.

China reported zero locally transmitted cases but several thousand imported cases. The efficacy of DHA-PIP remains high, and there is no confirmed AS resistance, but several K13 genotypes have been found, predominantly F46I. An “integrated TES” on imported cases has commenced in some provinces.

Piperaquine resistance can spread and emerge very fast; hence it was proposed to limit the use of DHA-PIP for GMS countries east of Bangkok. Regular monitoring of TES implementation must be intensified, including the testing of alternative ACTs in Cambodia, the Lao People’s Democratic Republic, Myanmar, Thailand and Viet Nam. iDES is an alternative option to TES only in areas far advanced in elimination with a primary objective, namely malaria elimination. Low dose PQ for Pf is not yet fully implemented in some countries, but it is a required core intervention for malaria elimination.
2.10 Updates from meeting on revised malaria treatment guidelines in the Western Pacific Region and challenges in South-East Asia Region GMS countries - Dr Rabindra Abeyasinghe and Dr Eva Christophel

The meeting informed countries of the need to scale up universal availability of quality-assured malaria diagnostic services and implementation of the revised WHO malaria treatment guidelines to facilitate achievement of this goal. The *Regional Action Framework for Malaria Control and Elimination in the Western Pacific 2016–2020* aims to further reduce malaria mortality by 50% by 2020, relative to the 2015 baselines.

Several key recommendations emerged from the meeting:

- Countries are encouraged to start full national implementation of the use of low-dose PQ for *P. falciparum* malaria as early as possible to further reduce transmission, which is especially urgent in countries reporting resistance to artemisinin and its partner drugs.
- Countries should conduct training and information dissemination campaigns to inform clinicians on the new treatment guidelines, which include the use of single-dose PQ for *P. falciparum* malaria to reduce transmission.
- Countries should strengthen malaria surveillance systems and use data for accurate quantification and logistics management to prevent stock-outs of ACTs.
- Countries are encouraged to start early implementation of PQ regimens to treat vivax malaria in view of the increasing proportion of vivax infections, including measures to ensure compliance with such regimens.

Myanmar NTG adhere to WHO recommendations for uncomplicated and severe malaria, including single-dose PQ after Pf ACT treatment. However, there are issues regarding unavailability of point-of-care G6PD testing, poor understanding regarding the prevalence of G6PD deficiency and its distribution, and no information on compliance to 14-day treatment with PQ in vivax cases.

Thailand 2015 NTG recommend DHA-PIP as the first-line drug against Pf, but pipeline stocks of ASMQ are still available in some facilities and are being used. Antimalarials are purchased by the government, but the logistic management system is not robust and does not include inventory from hospitals and general health system. While ~80% cases are *P. vivax*, there is no evidence of good compliance to 14-day or weekly PQ. Stock-outs (RDT, ACT and injectable AS) and focal outbreaks in some provinces over 2017 highlighted poor logistics management as well as clinical awareness and management of severe malaria among clinicians especially in the provinces where there is a high risk of importation.

**Update on *P. falciparum* ACT resistance molecular markers - Dr Benoit Witkowski**

Dr Witkowski presented the results of an analysis of molecular markers in the GMS: for artemisinin derivatives, the marker is K13 polymorphisms; for piperaquine, the marker is Pf plasmepsin 2-3 (Pfpms2-3); for mefloquine, the marker is pfmdr1 amplification. For lumefantrine and amodiaquine, markers are not yet established. The molecular signal of piperaquine resistance (PPQ-R) Pfpms2 amplification is based on strong signals of gene amplification in PPQ-R group in a region on chromosome 14, with two genes encoding haemoglobin-digesting proteases: Pf plasmepsins 2 & 3 (Pfpms2-Pfpms3). Pfpms2 amplification vs. *in vitro* data was also presented. In a recent study of 134 isolates collected in Cambodia, Pfpms2 amplification was evident in 67 out of 69 PPQ resistant parasites (2, 3 or 4 copies) and 1 out of 65 PPQ sensitive parasites. Pfpms2 amplification predicted parasite survival assay rates greater than 10% with a sensitivity of 97% and specificity of 98%. An assessment of Pfpms2 amplification versus clinical outcome also showed that of 725 patients, Pfpms2 CNV
and DHA-PIP treatment outcome association was observed in 119 treatment failures (from day 12 to day 42). Cumulative incidence of DHA-PIP treatment failure increased with the Pfpm2 copy number.

In order to know if true resistance is occurring, once a treatment failure has occurred, we need to determine if it is recrudescence or reinfection, and then whether it is an issue with dosage. The pharmacology studies show that piperaquine concentration in patients does not explain the treatment failures. In Viet Nam, where the molecular markers demonstrate a clear association between Pfpm2 amplification and treatment failure, there is no pfmdr1 amplification. Hence, ASMQ could be a good replacement treatment. Two exclusive resistance patterns with PPQ-R and mefloquine resistance (MQ-R) are evident, showing opposite susceptibility behaviour between the two drugs. Since it is impossible to have resistance to both at the same time, it may be possible to rotate these drugs. Preliminary results from molecular studies in the Lao People’s Democratic Republic in 2017 show that in the context of DHA-PIP treatment failures, the Pfpm2 amplification rate is elevated. For AL, treatment failure is not associated with pfmdr1 amplification and there is a need to find a relevant molecular marker. In summary, validated molecular markers are major assets in surveillance strategy. The Pfmdr1 amplification rate in Cambodia may change in the future. Finally, there is a need to find molecular elements linked to lumefantrine resistance.

3. PRESENTATION OF COUNTRY PLANS FOR TES
(COUNTRY PRINCIPAL INVESTIGATORS)

Cambodia

In 2018, Cambodia plans to conduct TES in six sites. AS-PYR will be tested in Kampong Speu and Pursat, while ASMQ will be tested in four sites: Mondokiri, Rattanakiri, Kratie and Kampong Thom. In 2019, AS-PYR will be tested in Rattanakiri, Stung Treng (for Pv and Pf), Kratie, Pursat and Kampong Speu. The TES implementers will be the CNM and IPC. Refresher microscopy training will be required and supervision will be provided on a monthly basis by the principal investigator (PI), co-PI supported by WHO.

China (Yunnan)

Technical support is required to develop the protocol for iDES in Yunnan. The approach is to: test DHA-PIP using the WHO-recommended dosage; refine the criteria for inclusion/exclusion; follow up schedule/end point; develop reporting forms/database; and sample collection for slides and molecular marker assays and monitoring activities. Additional technical support from WHO will be required for QA training of microscopists, establishment of the national slide bank, monthly monitoring from country PI and external monitoring from WHO. In Yunnan province, more than 90% of cases were imported from Myanmar, all confirmed by microscopy and RDT from passive case detection and active case detection (including asymptomatic and severe malaria cases).

Lao People’s Democratic Republic

In 2018 and 2019, the Lao People’s Democratic Republic plans to conduct TES for AL and ASMQ in Champassack Province and for AS-PYR in Savannakhet Province. The Center of Malariology, Parasitology and Entomology will be the TES implementer. Refresher microscopy training is required and supervision will be provided every two months by the PI and co-PI supported by WHO staff.
Myanmar

In 2018, Myanmar will conduct TES in the following sites: Tamu (Sagaing), testing DHA-PIP and CQ; Tabeik-kyin (Mandalay), testing AL, DHA-PIP and CQ; Paletwa (Chin), testing AL, DHA-PIP and AL in Pv; and Ingapu (Ayeyarwaddy), testing AL and CQ. In 2019, TES is planned for the following: Kachin, testing AL, AS-PYR (Pf & Pv); Northern Shan, testing AL, AS-PYR (Pf & Pv); Kayin, testing AS-PYR (Pf and Pv); and Tanintharyi, testing AS-PYR (Pf and Pv). The Department of Medical Research will implement TES, with monthly supervision by the PI, programme manager and WHO.

Thailand

In 2018, Thailand plans to conduct TES in Tak to test AS-PYR against Pf, and in Mae Hong Son to test CQ against Pv. In addition, iDES is planned on a national scale to test DHA-PIP. For 2019, TES is planned in Yala to test CQ against Pv, and iDES is planned on a national scale. The implementer will be the Bureau of Vector Borne Diseases (BVBD).

Viet Nam

Viet Nam plans to conduct TES in two provinces in 2018: Binh Phuoc and Dak Nong, both testing ASMQ. In addition, iDES is planned in five provinces to test DHA-PIP: Quang Tri, Gia Lai, Quang Binh, Khanh Hoa and Ninh Thuan. For 2019, TES is planned for three provinces: Binh Phuoc, testing ASMQ and CQ; Dak Nong, testing ASMQ; and Dak Lak, testing DHA-PIP. Also in 2019, iDES is planned for testing DHA-PIP in five provinces: Quang Tri, Gia Lai, Quang Binh, Khanh Hoa and Ninh Thuan. The implementer will be National Institute of Malariology, Parasitology and Entomology (NIMPE) and supervision will be provided by NIMPE and WHO. Other training needs include molecular training, Good Clinical Practice (Ministry of Health requirement) and microscopy.

India

For 2018, India proposes to test AL in the following cross-border sites: at the Bangladesh border, the four TES sites are West Garo Hills, Parganas North, South Garo Hills and Dhalai – two implemented by the National Institute for Malaria Research (NIMR) and two by the National Institute for Research in Tribal Health (NIRTH); at the Bhutan border, the TES sites are Kokrajhar and Udalguri; for the Myanmar border, the sites are Churchandpur and Lawngtlai, implemented by either NIRTH or NIMR at each of these sites; and at the Nepal border, AS+SP will be tested at Kheri site and the implementer will be NIRTH. In total there will be nine TES sites with a combined budget of US$ 345 897.

Partners comments

ACTMalaria: Ms Hugo extended her thanks to WHO for continuing to involve ACTMalaria in the TES meetings. She supported Dr Abeyasinghe’s input on QA as an essential factor against the spread of drug resistance in the region, and encouraged countries to establish QA systems, noting that the external competency system is only one component. She acknowledged the success of all countries in having WHO Level 1 microscopists and noted that now is the time to set up national competency assessment systems so that countries will have capacity to routinely assess their own microscopists. It is important to have this system in place not only because it is a requirement for elimination certification, but also because it should be a requirement in its own right. Ms Hugo was pleased to hear that the drug efficacy surveillance, initiated in 2014 by Malaysia to ensure no transmission after reaching 0 cases, was discussed now in detail. She encouraged participants to look at iDES not as another project but as something that will be implemented within the health system framework. In the future, only health facilities will have the capacity to continue monitoring and providing
diagnostics and treatment and should therefore be included in the QA framework. The WHO Framework for Malaria Elimination provides guidance on the implementation, for example, conducting case investigation/foci investigation, with strengthened capacities at health-facility level.

**USAID / President’s Malaria Initiative (PMI):** Dr Sintasath extended his thanks to WHO for organizing the meeting and thanked Dr Ringwald for his leadership and guidance through the process. He noted that the key issue currently being addressed is that of declining malaria in the context of malaria elimination. Therefore adjusting the current strategy and coming up with something useful for countries remains a priority for discussion. He noted that many questions remain, in terms of what the minimum requirements are for moving towards iDES. The countries that have already started this process, such as Thailand, may provide valuable examples from which to learn. The key issue now in other countries is to try to find enough malaria cases to conduct and complete TES because it is still critical in this region. He encouraged countries to continue their efforts and noted that it was very positive to see the decline in malaria overall. Dr Sintasath concluded by saying that now was the time to put in additional efforts, to implement TES more aggressively by expanding the networks to include more health facilities to recruit patients to be part of TES. Dr Sintasath thanked the Government of Viet Nam and the NMCP for hosting the meeting.

**4. CONCLUSIONS, NEXT STEPS AND RECOMMENDATIONS**

Dr Abeyasinghe applauded the dramatic reduction in cases across all countries but noted that gaps remain and efforts to eliminate malaria must be redoubled. There are still areas of high transmission, with an upsurge in malaria cases in 10 provinces in Cambodia, and in the southern province of Savanakhet in the Lao People’s Democratic Republic. As the transition from burden reduction to elimination continues, it will be important to look at whole system responses from TES to iDES. Strengthening surveillance to include case-based monitoring is a priority to ensure that every case is completely cured and parasite free. The numbers are low enough in many places to follow all cases. The best way to reach elimination is to strengthen surveillance of the disease and ensure at-risk populations are provided access to preventive interventions including quality-assured diagnostics and treatment. It is essential to prevent stock-outs of essential medicines and diagnostics. He extended his thanks to the Government of Viet Nam for kindly hosting the meeting and to all the participants for their contributions during the meeting.

Dr Christophel commented that the meeting was a catalyst for taking drug efficacy monitoring to a different dimension. Moving from TES to an integrated system would be of great benefit in the elimination phase. She reiterated the importance of laboratory quality assurance as a prerequisite for effective integrated surveillance. Dr Christophel commended the network as one of the strongest drug-resistance monitoring networks globally and applauded the commitment of all concerned. She then extended her thanks to Dr Ringwald and congratulated all partners for moving things forward. She reiterated WHO’s commitment to focus more on quality of treatment; surveillance and microscopy. The issues of substandard drugs as well as the availability of artemisinin monotherapies continue to be worrisome in the GMS. In December, a ministerial meeting of GMS countries will be held to accelerate the elimination of malaria in the region. This is a positive indication of countries’ commitment at the highest level.

Dr Ringwald congratulated participants on the success of the network meetings and all their achievements, echoing the comment that the GMS network is one of the more successful networks globally. He encouraged countries to be even more ambitious with TES – to extend
and increase. It would be important also to look at definitions of sentinel sites also at a provincial level. He noted the challenges of implementing iDES as it is only getting started, but he was confident that iDES would be the primary source of data in the near future. Finally, Dr Ringwald informed participants that he would be visiting countries more frequently to facilitate implementation of iDES.

4.1 Conclusions

1) Dramatic reductions in malaria cases across the GMS indicate that countries are making progress towards elimination despite reports of increasing resistance in several areas of the region. It was noted that in some countries, gaps in universal access to diagnosis and treatment are significant and must be addressed as a priority. All countries reported an increase in the proportion of *P. vivax* infections, with no uniform strategy on the use of PQ. While some countries do not use PQ for treatment of vivax, the ones that do use it have no information on compliance with PQ treatment.

2) Due to the concentration of cases along border provinces in many GMS countries, cross-border collaboration remains important in the GMS, particularly with porous borders and mobile populations. Proper tracking of patients is especially important when analysing data on the origin of cases to determine if infections are indigenous or imported. The implications for ensuring that appropriate treatment is given are significant, given the changes in national treatment guidelines.

3) ACT failures due to resistance to artemisinin and partner drugs remain a challenging issue in GMS countries, with four ACTs failing in Cambodia, and increasing evidence of partner drug failures in more provinces of the Lao People's Democratic Republic, Thailand and Viet Nam confirmed with K13 mutations and plasmepsin 2-3 (marker of piperaquine resistance). In Myanmar, the situation remains stable with partner drugs. Yunnan, China reported zero indigenous cases in 2017, and efficacy of first-line DHA-PIP was high among imported cases.

4) Alternative ACTs to current first-line treatments, such as A+M and/or AS-PYR (Pyramax™) are currently being tested in some countries. More information on presence and distribution of pfmdr1 and plasmepsin 2-3 copy numbers is required to better track resistance to partner drugs in the whole region.

5) The GMS has confirmed artemisinin resistance, so delayed parasite clearance is to be expected for all ACTs, while the same is not true for non-GMS countries (i.e. India and Bangladesh). There is an east–west divide. East of Bangkok, partner drugs were not working (ACT failures) and more than 90% C580Y mutations were observed; meanwhile, many patchy K13 markers with partner drugs having adequate efficacy (no ACT failures) was seen west of Bangkok.

6) As countries transition from burden reduction to elimination, it will be important to look at whole system responses and therefore to move from TES to iDES. Strengthening malaria surveillance in elimination settings including case-based surveillance will be important to ensure that every case is cured and parasite free. This is the desired endpoint of iDES, which is fundamentally different from the purpose of the current TES. Thus having a functional case-based surveillance system and a low enough number of cases to make full follow up of all cases possible will be the essential prerequisites to roll out iDES. Thailand commenced piloting iDES in several provinces and plans to scale it up nationwide in 2018.

7) Low-dose PQ for Pf is still not implemented in some countries although all countries have included it in their NTG. Administration of low dose PQ in all confirmed falciparum
cases is a priority to minimize the potential spread of resistant falciparum strains in the GMS.

8) Artemisinin monotherapies are still reportedly available in some countries and this remains a serious problem, as does the issue of sub-standard drugs. In addition, procuring adequate supplies of drugs (such as ASMQ) has become challenging when case numbers are low, as pharmaceutical companies either stop production or refuse to produce small amounts of a given drug. A potential solution to this issue is to explore the possibility of creating a virtual regional stockpile of antimalarials.

4.2 Recommendations

4.2.1 Recommendations for Member States

1) Countries are encouraged to continue their efforts in strengthening implementation of high-quality TES using the standard WHO protocol.

2) Countries should continue to strengthen laboratory capacities, particularly microscopy QA, as they move towards pre-elimination and elimination, while also strengthening microscopy QA for TES; and to implement quality control for molecular assays in collaboration with the regional reference laboratory at IPC.

3) Alternative ACTs need to be tested through TES before declining efficacy of current ACTs becomes apparent.

4) Countries are encouraged to monitor TES implementation closely in the sentinel sites using the WHO monitoring checklist to ensure adequate numbers of patients are enrolled.

5) As countries move towards elimination, a strong surveillance system needs to be in place to facilitate integration of drug efficacy monitoring into routine surveillance.

4.2.2 Recommendations for WHO

1) WHO will continue to provide technical assistance in TES and iDES implementation, to share information on artemisinin resistance in the GMS and to provide guidance on national and regional drug policy reviews.

2) WHO will revive the discussion about a regional drug stockpile at the next Regional Steering Committee meeting. A regional drug stockpile would be a potential solution to stock-outs and encourage drug companies to continue to produce greater quantities of these drugs.

3) WHO is requested to continue providing support for countries moving into elimination settings, particularly as they transition to iDES.

4) Therapeutic efficacy surveillance for ACTs already being used in countries as part of NTG will no longer require ethical clearance as it will be considered as a part of overall surveillance.
# ANNEX 1

## TES Country Plans, 2017-2018

<table>
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<tr>
<th>Name of site</th>
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<th>Proposed budget</th>
<th>Name of site</th>
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### LAO PDR

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# AGENDA

**Day 1: Thursday, 28 September 2017**

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<tr>
<th>Time</th>
<th>Session</th>
<th>Speaker(s)</th>
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<tr>
<td>08:00 – 08:30</td>
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| 8:30 – 09:30 | Opening Session                                                                               | Dr. Rabindra Abeyasinghe, Coordinator, WPRO/MVP (on behalf of the Regional Director, WHO Western Pacific Region)  
Dr. Le Thanh Dong, Director, IMPE HCM  
Meeting objectives  
Self-introduction of participants and observers  
Nomination of the Chair and Rapporteur  
Administrative announcements |                                                                                                       |
| 09:30 – 10:00 | **Group photograph followed by coffee/tea break**                                              | Dr. Rabindra Abeyasinghe  
Dr. Maria Dorina Bustos, Malaria Technical Officer                                                                 |
| 10:00 – 10:30 | Session 1: Regional updates                                                                  | Dr. Maria Dorina Bustos  
Dr. Hiromasa Okayasu, Coordinator, Mekong Malaria Elimination (MME) Program  
Anti-malarial drug resistance monitoring in the Greater Mekong Subregion: progress and implementation challenges; QC monitoring |                                                                                                       |
| 11:00 – 11:30 | Session 2: Country Presentations from Greater Mekong Subregion TES (15 min country presentation, followed by discussion) | Dr. Maria Dorina Bustos  
Plenary Discussion  
Lunch break |                                                                                                       |
| 13:00-15:30 | Cambodia  
Lao PDR  
Myanmar  
Viet Nam  
Thailand | CNM TES Principal Investigator  
CMPE TES Principal Investigator  
DMR TES Principal Investigator  
NIMPE TES Principal Investigator  
BVBD TES Principal Investigator |                                                                                                       |
| 15:30-15:45 | **Coffee / tea break**                                                                        |                                                                                                       |
| 15:45 – 17:00 | Session 3: Integrated drug efficacy surveillance                                              | Dr. Pascal Ringwald, Coordinator, Drug Efficacy and Response, Global Malaria Programme  
Recommendations on integrated monitoring of drug efficacy in surveillance in the context of elimination |                                                                                                       |
<p>| 18:00 – 19:30 | Reception dinner (Hotel venue)                                                                 |                                                                                                       |</p>
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<th>Time</th>
<th>Session/Session Type</th>
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<tr>
<td>8:30 – 9:00</td>
<td>Session 4: Country presentations from SEARO</td>
<td>India</td>
<td>TES principal Investigators</td>
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<td>9:00-9:30</td>
<td>Session 4: Country presentations from SEARO</td>
<td>Summary of country results (GMS countries, Bangladesh and India)</td>
<td>Dr Eva Christophel, Regional Adviser Malaria Department of Communicable Diseases, SEARO</td>
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<td>9:00 – 9:30</td>
<td>Session 5: Updates on antimalarial resistance</td>
<td>Updates from the meeting on revised treatment guidelines meeting for malaria endemic countries of WPR – Q &amp; A</td>
<td>Dr Rabindra Abeyasinghe</td>
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<td>10:00 – 10:30</td>
<td>Session 5: Updates on antimalarial resistance</td>
<td>Updates on Kelch 13, P14 and other molecular markers for resistance in the GMS – Q &amp; A</td>
<td>Dr Benoit Witkowski, Institut Pasteur du Cambodge</td>
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<td>10:30 – 11:00</td>
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<td><strong>COFFEE / TEA BREAK</strong></td>
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| 11:00 – 12:00| Session 5: Planning and budget: TES, TES + MM, integrated monitoring drug efficacy in surveillance | • Introduction to Group Work  
• Country breakout groups: 2018-19 country TES or Drug Resistance Surveillance plans and budgets | Dr Maria Dorina Bustos Facilitators (WHO staff) |
| 12:00 – 13:00|                                           | **LUNCH BREAK**                                                                                   |                   |
| 13:00 – 14:00|                                           | Group Work continued                                                                             |                   |
| 14:00 - 15:30| Session 6: Presentation of GMS Country plans | Plenary presentations and discussion of country plans / drug resistance surveillance and budget (10 mins / country); Q & A  
- Cambodia  
- China (Yunnan)  
- Lao People's Democratic Republic  
- Myanmar  
- Thailand  
- Viet Nam | Country TES Principal Investigators |
| 15:30 – 16:00|                                           | **COFFEE/TEA BREAK**                                                                               |                   |
| 16:00 – 16:30|                                           | Partners' comments: ACTMalaria, USAID/PMI                                                         |                   |
| 16:30 – 16:45| Session 7: Next Steps & closing            | Conclusion, next steps and recommendations                                                         | Dr Rabindra Abeyasinghe  
Dr Eva Christophel  
Dr Pascal Ringwald |
| 16:45 – 17:00|                                           | Closing                                                                                           | Dr Eva Christophel, WHO SEARO |
LIST OF PARTICIPANTS

1. COUNTRY PARTICIPANTS

Dr Chea Huch, Vice Director, National Center for Parasitology, Entomology and Malaria Control, Corner Street 92-93, Trapeng Svay Village, Phnom Penh, Cambodia, Tel No. +855 10 316 306, Email: huch@cnm.gov.kh

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