MEETING REPORT

FORUM ON OPERATIONAL RESEARCH IN THE CONTEXT OF THE LAST MILE OF MALARIA ELIMINATION IN GREATER MEKONG SUBREGION COUNTRIES

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NOTE

The views expressed in this report are those of the participants of the Forum on Operational Research in the Context of the Last Mile of Malaria Elimination in Greater Mekong Subregion Countries and do not necessarily reflect the policies of the conveners.

This report has been prepared by the World Health Organization Regional Office for the Western Pacific for Member States in the Region and for those who participated in the virtual Forum on Operational Research in the Context of the Last Mile of Malaria Elimination in Greater Mekong Subregion Countries from 24 to 25 November 2020.
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Keywords:
Guideline / Malaria – prevention and control / Mekong valley / Operations research
ABBREVIATIONS

ACT  artemisinin-based combination therapy
AFRIMS  Armed Forces Research Institute of Medical Sciences
EASIMES  Environment analysis and surveillance to improve malaria elimination strategies project
G6PD  glucose-6-phosphate dehydrogenase
GMP  WHO Global Malaria Programme
GMS  Greater Mekong Subregion
hsRDT  highly sensitive rapid diagnostic test
LLIN  long-lasting insecticidal net
MDA  mass drug administration
MME  WHO Mekong Malaria Elimination programme
MORU  Mahidol-Oxford Tropical Medicine Research Unit
NMP  national malaria programme
PCR  polymerase chain reaction
PSI  Population Services International
RACD  reactive case detection
RAI  Regional Artemisinin-resistance Initiative
RCAF  Royal Cambodian Armed Forces
RDT  rapid diagnostic test
rMMDA  reactive focal mass drug administration
SMRU  Shoklo Malaria Research Unit
UCSF  University of California, San Francisco
WHO  World Health Organization
SUMMARY

The World Health Organization Mekong Malaria Elimination (MME) programme hosted the virtual Forum on Operational Research in the Context of the Last Mile of Malaria Elimination in Greater Mekong Subregion Countries from 24 to 25 November 2020. The Forum brought together participants from the six Greater Mekong Subregion (GMS) countries – Cambodia, China (Yunnan Province), Lao People’s Democratic Republic, Myanmar, Thailand and Viet Nam – and the Global Malaria Programme (GMP), as well as technical experts, researchers and partners to present and discuss recent findings relevant to malaria elimination in the GMS.

The operational research presented in the Forum focused on improving the uptake and scale-up of malaria elimination programming, cost-effectively implementing combinations of interventions, and measuring intervention success and impact. The main discussion points included research projects related to various programmatic areas including case detection, diagnosis, treatment, prevention, the efficacy of antimalarial drugs, vector control, radical cure, testing, surveillance, epidemiology and transmission.
1. INTRODUCTION

1.1 Background

The six countries of the Greater Mekong Subregion (GMS) launched a malaria elimination strategy in 2015 that aims to eliminate Plasmodium falciparum malaria by 2023 and all forms of malaria by 2030. Heads of states at the East Asia Summit made a similar commitment in Myanmar in November 2014 to eliminate the disease from the Asia Pacific region by 2030. Furthermore, GMS health ministers signed the Ministerial Call for Action to Eliminate Malaria in the Greater Mekong Subregion before 2030 at the World Health Assembly in May 2018 in Switzerland. Through this agreement, they committed to working together with relevant entities to ensure that all research efforts are nationally coordinated, adhere to international standards and to translate operational research findings into policy and action.

WHO has emphasized the importance of operational research as an integral part of malaria elimination programmes. In the past decade, the funding and the development of malaria research in the GMS have resulted in impressive improvements in malaria control and has supported efforts to monitor drug resistance. To provide timely results to inform policy making and project implementation, the Bill & Melinda Gates Foundation provided funding to WHO to host the Forum on Operational Research in the Context of the Last Mile of Malaria Elimination in Greater Mekong Subregion Countries. The Forum was convened to provide timely results for policy-making and project implementation.

1.2 Meeting objectives

The objectives of the meeting were:

1) to define optimal and sustainable approaches for malaria prevention, diagnosis and treatment (such as):
   • radical cure of P. vivax;
   • integrating malaria elimination into health systems; and
   • adapting tools and addressing barriers to prevention, diagnosis and treatment.

2) to accelerate the transition from malaria control to elimination and beyond by:
   • accelerating malaria elimination; and
   • reaching and sustaining malaria elimination.

2. PROCEEDINGS

2.1 Opening session

2.1.1 Opening ceremony

Dr Ailan Li, WHO Representative, Cambodia, delivered the welcome address to the workshop participants. In the welcome speech, she emphasized the importance of operational research as an integral part of disease control programmes. Following this, Dr Luciano Tuseo, Coordinator of the MME programme, provided a briefing of the meeting objectives. This was followed by the nomination of Dr Lek Dysoley, Deputy Director of the National Center for Parasitology, Entomology and Malaria Control, Cambodia, as the chair of the meeting and Dr Pascal Ringwald, Coordinator from the WHO GMP, as the meeting moderator.

2.1.2 An update on the development of malaria elimination guidelines

Dr Kimberly Lindblade, Team Leader for the Malaria Elimination Unit within the GMP, provided an update on the development of malaria elimination guidelines. WHO developed new guidance for malaria elimination in 2017. The Framework for Malaria Elimination encourages all countries to
accelerate towards malaria elimination. It provides a clear and simplified process for WHO certification of malaria elimination.

The development of new guidelines includes eight steps:

1. Creating an overview of the process of guideline development
2. Setting up the external guideline development group
3. Formulating the PICO (population, intervention, control, and outcomes) questions and selection of outcomes to define the questions
4. Retrieving evidence, including quality assessment and synthesis
5. Grading the evidence with a process called GRADE to assess the certainty of the evidence
6. Formulating recommendations
7. Conducting an external review
8. Disseminating the guidelines in the field for the national malaria programmes (NMPs) to incorporate in their implementation frameworks, followed by an evaluation to measure the impact of the implementation.

The proposal for elimination recommendations was made to the Malaria Policy Advisory Committee in 2019, and WHO received an endorsement to move forward with nine questions on elimination including the use of mass drug administration (MDA), reactive case detection (RACD), reactive focal mass drug administration (rfMDA) and other strategies. At this stage, protocols for systematic reviews and meta-analysis of evidence are being developed. WHO will be combining the existing guidelines (vector control and case management) into consolidated malaria guidelines that WHO will publish in January 2021. By June 2021, WHO will add new recommendations for elimination to the consolidated guidelines.

During the discussion, Dr Lindblade highlighted that there is a distinction between WHO guidance and guidelines. Guidelines are developed through a rigorous framework that follows a review of evidence. Once completed, the Malaria Elimination Guidelines will be recognized as WHO’s official approach.

2.2 Session 1: Mass drug administration in the context of Greater Mekong Subregion countries, targeted drug administration and forest malaria prophylaxis

2.2.1 Targeting high-risk populations with enhanced reactive case detection: a study to assess the effectiveness and feasibility for reducing *Plasmodium falciparum* and *Plasmodium vivax* malaria in southern Lao People’s Democratic Republic and Thailand

Dr Timothy Finn, University of California, San Francisco (UCSF), presented information about their study in Thailand and the south of the Lao People’s Democratic Republic to assess the effectiveness and feasibility for reducing *P. falciparum* and *P. vivax* malaria. RACD is a widely practised method to identify infections at the community level after passive index case detection. The UCSF has initiated the COMBAT Trial (community-based active case detection and treatment), which includes three main activities:

1. an impact evaluation of enhanced RACD in the Lao People’s Democratic Republic and rfMDA in Thailand targeting village-based populations and forest workers;
2. an assessment of the feasibility and acceptability of community-based RACD and rfMDA; and
3. an assessment of the operational feasibility of conducting glucose-6-phosphate dehydrogenase (G6PD) testing, referral, and treatment adherence among positive *P. vivax* rapid diagnostic test (RDT) cases.

In the Lao People’s Democratic Republic, the trial will assess the effectiveness, cost-effectiveness, safety, acceptability, and operational feasibility of community-led malaria RACD using highly sensitive RDTs (hsRDTs) targeting both village-based populations and high-risk forest workers. The COMBAT platform was amended in June 2020 to include quantitative G6PD testing. This is the first quantitative testing pilot in the country and will inform future expansion under Regional Artemisinin-resistance Initiative (RAI)3E funds.
At the same time, the UCSF is conducting an assessment of enhanced rMDA in Thailand. The research will evaluate the effectiveness of enhanced rMDA, targeting both village and forest working populations, for reducing the incidence and prevalence of *P. falciparum* and *P. vivax* within four provinces in Thailand. The study findings will provide relevant programmatic information on the operational feasibility and acceptability of rMDA for *P. falciparum* and *P. vivax* as a response strategy in active foci.

The field research in both countries was extended due to implementation delays related to the coronavirus disease 2019 (COVID-19) pandemic and will continue for another year. During the discussion, Dr Finn mentioned that RDTs were included in the study to pick up any additional positive cases. However, this inclusion has not provided much added data to the ongoing studies.

2.2.2 Minimizing the risk of malaria among forest goers in the Greater Mekong Subregion: a randomized controlled trial to estimate the efficacy and feasibility of a forest malaria prophylaxis over one month

Professor Richard Maude presented preliminary findings from the Mahidol-Oxford Tropical Medicine Research Unit’s (MORU) studies on the efficacy and feasibility of a forest malaria prophylaxis intervention in Cambodia, Thailand and the Lao People’s Democratic Republic. The study aims to:

1. better understand the epidemiology of forest malaria in selected high-risk areas;
2. assess the potential efficacy of antimalarial prophylaxis for high-risk forest goers to help accelerate elimination; and
3. determine the acceptability and feasibility of chemoprophylaxis as an intervention for high-risk forest goers.

In Cambodia, the prophylaxis trial covered adults staying overnight in the forest among the villages with malaria cases in Steung Treng. The study was unblinded, individually randomized and controlled, and participants were either given artemether-lumefantrine or multivitamins twice daily for three days, followed by two doses weekly. They were followed up every 28 days as they continued to visit the forest. The trial mapped participants’ travel in the forest to identify potential transmission sites.

In-depth interviews are also being conducted among forest goers, community leaders, health-care workers and policy-makers in Cambodia, the Lao People’s Democratic Republic and Thailand to assess the potential feasibility of prophylaxis in each country.

The initial findings from the trial indicate that the acceptability and adherence for artemether-lumefantrine chemoprophylaxis were very high in Cambodia. Trust and communication were important factors to motivate forest goers to join the study and take prophylaxis. MORU noted that there should be a good explanation of the mechanism, benefits and limitations, as well as the need to continue using the other protection methods. Recruitment is ongoing, and further trial and feasibility results are pending.

During the discussion, Professor Maude noted that adverse drug reactions are monitored through contacts, self-reporting and follow-up visits. Forest goers were not provided packages in addition to the prophylaxis intervention.

2.2.3 The impact of targeted malaria elimination with mass drug administrations on *Plasmodium falciparum* malaria in Southeast Asia: a cluster randomized trial

Dr Lorenz von Seidlein outlined MORU’s study on the impact of targeted malaria elimination MDA on *P. falciparum* malaria in Southeast Asia. More than 8000 people participated in the study across study sites in Cambodia, the Lao People’s Democratic Republic, Myanmar and Viet Nam (4135 in intervention villages, and 4310 in control villages). Everyone was equipped with basic malaria control measures, which included early diagnosis and treatment, bed nets and community engagement. The intervention villages received a full three-day course of dihydroartemisinin-piperaquine in three rounds.
Dr von Seidlein noted that great emphasis was placed on community engagement. The success of MDAs depends on the efficacy of the drug regimen, the coverage of the target population and local malaria epidemiology. Examples for community engagement included drama shows in Cambodia and community incentives in the Lao People’s Democratic Republic.

The intervention findings indicate that the MDAs were well tolerated and safe. The study achieved 87% coverage for at least one round and 57% for all three rounds. *P. falciparum* prevalence dropped initially but some rebound was observed. Despite resistance, dihydroartemisinin-piperaquine cleared 94% of infections. MDA with schizontocidal drugs had only a transient effect on *P. vivax* infections. Therefore, MORU suggested that a radical cure with an 8-aminoquinoline will be needed for the rapid elimination of *P. vivax* malaria.

Dr von Seidlein concluded that MDA is potentially a useful tool for accelerating *P. falciparum* elimination. To maximize the impact, MDAs have to be implemented in large areas to minimize the immediate reimportation of *P. falciparum*. The optimal drug combination is site-specific and has to be adapted to local antimalarial susceptibility patterns. Lastly, very high coverage is essential for success and considerable resources are required to engage entire communities to participate in MDAs.

During the discussion, Dr von Seidlein emphasized that the effectiveness of the different community engagement strategies depends on trust-building exercises, which are adapted to a specific community. It is important that a focal point is available in the targeted sites to answer questions and provide medical support after the MDA.

2.2.4 Deployment of malaria elimination interventions in high-risk military populations: challenges and new opportunities

Dr Mariusz WojnarSKI delivered a presentation on the research findings from the Armed Forces Research Institute of Medical Sciences (AFRIMS) on malaria elimination strategies of the Royal Cambodian Armed Forces (RCAF). The study sought to define effective, appropriate and implementable strategies for malaria elimination in military forces in Cambodia. The three pillars of ongoing efforts include the selection of the most suitable chemoprophylaxis and implementation of insecticide treated uniforms, research on G6PD diagnostcs, and the implementation of the pharmacovigilance for safe use of radical cure interventions. Based on studies completed by AFRIMS, the rapid decline of *P. falciparum* malaria was possible to achieve with the available tools. However, breakthrough infections were frequent in the context of dihydroartemisinin-piperaquine resistance and targeted interventions were not effective for *P. vivax* elimination. In 2020, AFRIMS observed an overall decline of malaria cases in the RCAF, similar to the observations made in the civilian sector.

The current efforts focus on the deployment of chemoprophylaxis at the highest-risk military camps, utilizing the latest ACTs, namely artesunate-pyronaridine to overcome the limitations of dihydroartemisinin-piperaquine drug resistance. Other efforts include the optimization of available tools for *P. vivax* elimination (i.e. shorter courses of primaquine and assessing the utility of other drugs such as tafenoquine). It was highlighted that the use of tafenoquine will come with a number of challenges in the Cambodia context. Despite approval from the Food and Drug Administration, tafenoquine is not pre-qualified by WHO or available in Cambodia; it requires reliable G6PD quantitative tests. The combination of tafenoquine with certain ACTs is known to be less effective, and tafenoquine has not been evaluated in combination with artesunate-mefloquine or artesunate-pyronaridine.

Despite disruptions caused by the COVID-19 pandemic, the RCAF continues to make progress in malaria elimination efforts. The military was provided with personal protective equipment and G6PD diagnostics and haemolysis training in support of pharmacovigilance. The novice trainees (medics) were able to acquire the necessary skills to perform the G6PD screening tests independently. The treatment algorithms developed for medics to support of radical cure deployment were well received by RCAF. A formal evaluation process was put in place to minimize potential risks with radical cure
deployment. Further training was delivered on the detection of adverse events related to the use of pyramax or primaquine. Dr Wojinarski highlighted that there is strong support by the RCAF medical department to develop a unique set of tools for malaria elimination that are tailored for their setting. The case study shows that chemoprophylaxis and vector control measures must target high-risk groups. The G6PD diagnostic tests are ready to be deployed in the military by the trained medics. However, the military needs to strengthen pharmacovigilance systems due to the potential for misclassification of G6PD in a subset of treated subjects, which is a limitation of the available tests.

2.2.5 Will ivermectin mass drug administration help eliminate residual malaria in the Greater Mekong Subregion?

Dr Kevin Kobylinski, AFRIMS, outlined how ivermectin MDA could potentially help eliminate residual malaria in the GMS. Most malaria vectors in the GMS are outdoor-feeding (exophagic), outdoor-resting (exophilic) or feed before bedtime (crepuscular). Most malaria transmission in the GMS occurs in forested areas where people are less protected and not in the village home. Therefore, vector control measures need to account for human and vector behaviour. Mahidol University and AFRIMS will complete an ivermectin MDA field study in rubber plantations in southern Thailand. It will target Anopheles minimus, which are ivermectin-sensitive and the primary malaria vector.

Existing research on ivermectin usage has shown a clear effect on vector populations and reduced clinical incidence among humans. If used on livestock, ivermectin MDA has been linked to increases in weight gain and milk yields. Long-lasting formulations have a much longer drug half-life compared to humans. However, the disadvantages for human use is that it likely requires monthly administration and no other mosquito-lethal endectocides have been approved for human use. In terms of livestock, ivermectin use for animals lacks published field trials, and it does not guarantee an effect against human-feeding vectors. It likely requires multiple administrations, and there is a possibility of resistance development. However, ivermectin treatment of humans and livestock should not be viewed as competing approaches but should be used in combination, if justified.

During the discussion, Dr Kevin Kobylinski emphasized that the standard ivermectin slaughter withdrawal period following treatment for cattle is 35 days and for swine 18 days; long-lasting formulations have even longer withdrawal periods.

The GMP noted that ivermectin constitutes a new paradigm in malaria vector control. Ivermectin is an exciting new potential intervention and will be reviewed by several groups at WHO, including the prequalification team and the Vector Control Advisory Group. Additional reviews for drug safety may also be needed.

2.3 Session 2: Radical cure for Plasmodium vivax (testing and community-level implementation)

2.3.1 Effectiveness of novel approaches to radical cure with tafenoquine and primaquine

Professor Richard Price, Menzies School of Health Research, delivered a presentation on the effectiveness of novel approaches to radical cure for P. vivax malaria. WHO recommends primaquine (for 14 days) for patients with normal G6PD activity in areas where frequent relapsing strains of P. vivax are prevalent. However, the risk of acute haemolysis in patients with G6PD deficiency and need for supervision over a 14-day period means that primaquine is often not prescribed for P. vivax malaria. The IMPROV (improving the radical cure of P. vivax malaria) multicentre clinical trial evaluated the safety and efficacy of a 7-day primaquine regimen compared with a 14-day primaquine and placebo regimen (short-course primaquine trial). The IMPROV study demonstrated that a high dose 7-day primaquine (PQ7) treatment was safe, highly effective (>88%) and non-inferior to 14-day primaquine (PQ14) in patients with normal G6PD. Clinical trials (DETECTIVE) have also been conducted for tafenoquine coadministered with chloroquine for the treatment and relapse prevention of P. vivax malaria. These trials indicated that tafenoquine coadministered with chloroquine indicated that was more efficacious than chloroquine alone, although the risk of recurrence was still 30–40% at one year.
There are risks of haemolysis in G6PD deficient patients, but there are also many benefits to primaquine radical cure. In a hospital-based cohort study in Papua, Indonesia (published in 2020), patients who received radical cure with PQ14 even without prior G6PD testing demonstrated a lower risk of hospital admission and lower mortality. Professor Price reiterated that it is not possible to prevent every case of severe haemolysis, but early observation following acute treatment is warranted to identify haemolysis early and curtail treatment before severe symptoms develop. Although primaquine at the correct dose is safe and highly effective in preventing *P. vivax* relapse, in most patients, heterogeneity in patient populations demands that policy and practice is tailored to the local environment, needs and resources.

2.3.2 Implementation and evaluation of a model of care of glucose-6-phosphate dehydrogenase activity testing and primaquine for *Plasmodium vivax* radical cure in Cambodia and (VIGTARC study)

Professor Shunmay Yeung delivered findings on the VIGTARC study (*P. Vivax* G6PD testing and radical cure study in Cambodia), a collaborative implementations research project between the Center for Health and Social Development in Cambodia, the London School of Hygiene & Tropical Medicine and the Cambodian National Center for Parasitology, Entomology and Malaria Control. VIGTARC aims to implement and evaluate a new model of care for G6PD testing and primaquine for the radical cure of *P. vivax* infections. The project was launched in 2019 and is ongoing in the four highest-burden health centres in Pursat Province, Cambodia. Leveraging the existing network of village malaria workers, patients with RDT-confirmed *P. vivax* infections are referred from the community to the local health centre where they receive a G6PD test. According to the test result, treatment with primaquine is initiated, with referral back to the village malaria workers for follow-up in the community to check for side-effects and ensure adherence. Continuity of care and malaria surveillance has been supported electronically through the development and implementation of a *P. vivax* module integrated into the existing Malaria Information Surveillance app, accessed on tablets at the health centres and on smartphones provided to the village malaria workers. Over 480 patients have been tested for G6PD deficiency and over 400 treated with primaquine. Quantitative and qualitative analysis are ongoing but have indicated that the new model of care is feasible and highly acceptable in this setting. Primaquine was generally very well tolerated, and, with community support, high levels of adherence to the 14-day regime were achieved.

2.3.3 Utilizing existing tools for *Plasmodium vivax* elimination

Dr Cindy Chu, Shoklo Malaria Research Unit (SMRU), presented an overview of existing tools for *P. vivax* elimination. The presentation provided an assessment of G6PD testing in advance of MDA as well as at the time of drug administration or RDT. The advantage of G6PD testing in advance of MDA is that it can be combined with malaria screening through ultrasensitive PCR tests. Teams can also focus on engagement with screening activities, organize how the treatment should be managed and plan for future MDA visits. The disadvantage of this approach is that it requires two visits and a G6PD retention back-up plan, and it only treats ultrasensitive PCR positive cases. On the other hand, G6PD at the time of drug administration or RDT can be completed in one visit and allows for immediate treatment after the G6PD test. The shortcoming of this approach are that this provides less ability to plan ahead and there potentially would be no epidemiological survey to inform programming. Each of these methods presents different advantages and disadvantages for *P. vivax* elimination, and they need to be applied in consideration of the operational context. SMRU highlighted that combining these tools offers a promising framework to eliminate *P. vivax* malaria.

2.4 Session 3: New malaria antivectorial tools

2.4.1 Assessing the relationship between long-lasting insecticidal net material and long-lasting insecticidal net usage in Myanmar and Cambodia

Dr Si Thu Thein, Population Services International (PSI), Myanmar, presented a study on the relationship between long-lasting insecticidal net (LLIN) fabric material and LLIN usage in Cambodia and Myanmar. The study was a cross-sectional household survey aimed at providing a better understanding on the actual use of LLINs according to the material (as opposed to only the LLINs
preferred choice of the implementer or target population). The study concluded that when households had both types of nets, polyester LLINs were more likely to be used than polyethene ones in both countries. However, the overall usage was similar between the households if they had only one type of LLIN.

2.4.2 Myanmar Private Sector Antimalarial Outlet Survey 2019

Dr Ye Kyaw Aung presented PSI Myanmar’s 2019 cross-sectional assessment of the antimalarial drug landscape in Myanmar. The Private Sector Antimalarial Outlet Survey aims to assess provider readiness for quality malaria case management by measuring data on the availability of antimalarial medication, diagnostics, providers’ training capacity, record keeping and regulatory visits. The availability of antimalarial medicine, especially quality-assured artemisinin combination therapy (ACT), and RDTs was higher among private facility and health workers than other types of private outlets (pharmacies, itinerant drug vendors and trained health providers). The availability of oral artemisinin monotherapy has declined significantly over recent years; very few pharmacies and trained health providers stock the product. The majority of all outlets (except health workers) were not actively engaged with the NMP for malaria case management and reporting, (particularly pharmacies, itinerant drug vendors, and health facility clinics).

2.5 Session 4: Health system strengthening: integration of malaria community health workers

2.5.1 Optimal community-delivered malaria elimination models for the Greater Mekong Subregion

Dr Win Han Oo presented the Burnet Institute's research on optimal community-delivered malaria elimination models for the GMS. The mixed-methods multi-country operational research project aimed to produce a community-delivered malaria elimination model that is acceptable, operational, pragmatic, and cost-effective across GMS countries. Different integrated community-delivered models have been developed, piloted and evaluated globally. The integrated community malaria volunteer (or ICMV) model is the current standard of care in Myanmar and the volunteer malaria worker model in other GMS countries. While the malaria volunteers mainly focus on control and elimination of malaria, the integrated community malaria volunteers undertake additional screening and referral services for a range of other diseases, including dengue, lymphatic filariasis, tuberculosis, HIV/AIDS and leprosy, on top of malaria. The Burnet Institute and its partner, the Lao Tropical and Public Health Institute, conducted qualitative community and stakeholder consultations in Myanmar and the Lao People’s Democratic Republic to determine an appropriate model for the GMS. The findings have led to the adaptation of a community-delivered integrated malaria elimination or CIME model, which will be field tested and evaluated in Myanmar in 2021. It integrates interventions for malaria elimination such as malaria diagnosis using RDTs, treatment, referral and reporting, prevention interventions (behaviour change communication, net and repellent distribution), assisting in case and foci investigation, larval source management, and prevention and referral services for dengue, tuberculosis, childhood diarrhoea and RDT-negative fevers. It involves recruiting and training a volunteer to implement the model in each village who will be supervised and monitored by basic health staff at least monthly.

The Burnet Institute concluded that the malaria volunteer model needs to be transformed into an integrated model preferred by the community and acceptable by the health ministry of the respective country. The community-delivered integrated malaria elimination model(s) in the GMS should be effective model(s) in primary health care and support the achievement of universal health coverage. This transformation is crucial to ensure high rates of community testing in the elimination phase and maintain volunteers’ social motivation.

2.5.2 Reactive and proactive case detection for the elimination of malaria in Cambodia forest goers (PACES study)

Professor Shumay Yeung presented results from PACES, a mixed-methods study undertaken as a collaboration between the London School of Hygiene & Tropical Medicine, the Center for Health and Social Development, the Cambodian National Center for Parasitology, Entomology and Malaria Control, Institut Pasteur du Cambodge and other partners. The study took place in Oddor Meanchey
and involved 14 health centres and 130 villages and their village malaria workers. Household, forest-going neighbours and forest-going “co-travellers” of confirmed symptomatic *P. falciparum* index cases were screened for malaria using RDTs and real-time PCR. Confirmed cases of *P. falciparum* and *P. vivax* were treated with artesunate and mefloquine as per national guidelines. The study confirmed that malaria infection in this setting is highly focal (only found in 15 out of 130 villages at baseline) and dominated by *P. vivax*. It also found that screening for asymptomatic carriers based on recent forest-going yielded the highest positivity rates and that the pick-up was low using reported or measured fever and in non-forest going household contacts. In the first field assessment of ultra-sensitive RDTs in the region, the study also showed that they were not more sensitive than standard RDTs for detecting asymptomatic *P. falciparum* infection. Finally, a qualitative sub-study provided a detailed description of forest-goers in the area and documented that for affected communities the relapsing nature of *P. vivax* poses more of a burden than *P. falciparum*.

### 2.6 Session 5: Surveillance and malaria elimination

#### 2.6.1 Using highly sensitive rapid diagnostic tests compared to control for reducing the health centre catchment and village-level prevalence and incidence of *Plasmodium falciparum* among village residents and mobile and migrant and other high-risk populations in Champasak Province, southern Lao People’s Democratic Republic

Dr Timothy P Finn, UCSF, delivered a presentation on the use of hsRDTs to measure *P. falciparum* incidence among village residents and mobile and migrant and other high-risk populations in Champasak Province, Lao People’s Democratic Republic. The interventions included village-based mass test and treat (or MTAT), focal test and treat (or FTAT) in high-risk populations, and the combination of these approaches, using hsRDTs. In this study, the performance of the hsRDT and the conventional RDT were nearly identical, for identifying current infections. Diagnostic sensitivity remains an issue for active surveillance approaches, especially for *P. vivax* parasites.

#### 2.6.2 Environment analysis and surveillance to improve malaria elimination strategies (EASIMES)

Dr Florian Girond and Dr Jordi Landier presented SMRU’s research project in eastern Myanmar on environment analysis and surveillance to improve malaria elimination strategies (EASIMES). The project aims to reinforce the microstratification and active surveillance tools used by NMPs to allocate resources and target interventions during their control and elimination efforts. The project has investigated the relationship between the forest environment and malaria by developing a regional early warning system that can be generalized at the national scale. It involves the development of an accurate land-use/land-cover (or LULC) database from remote-sensing data confirmed by field surveys (ground-truthing). This LULC map characterizes the environments around villages and locations where people move and is integrated with malaria data (human incidence/prevalence; vector diversity and abundance) to analyse and predict malaria risk. It also integrates malaria- and vector-risk data to inform microstratification on potential risks of persistence or resurgence of malaria. The findings showed that distance gradients to a midland climate and dense forests explain more than 50% of *P. falciparum* variance. The analysis of the relationship between dynamic profiles and environmental factors is ongoing. A malaria environmental surveillance system is live and will be further developed.

#### 2.6.3 Effectiveness of repellent delivered by village health volunteers in Myanmar

Professor Freya Fowkes presented findings from the Burnet Institute’s study on the effectiveness of personal repellents delivered through village health volunteers on malaria incidence in villages in south-east Myanmar. Between April 2015 and June 2016, the Burnet Institute’s randomized 116 villages in Myanmar to distribute repellent through village health volunteer networks using a stepped-wedge cluster randomized controlled trial design and followed the villages up for 15 months to detect malaria by RDT and highly sensitive polymerase chain reaction (PCR). The distribution of repellent through the village health volunteer network did not reduce RDT-detectable infections (due to the smaller than expected number of RDT-detectable infections) but reduced the odds of PCR-detectable infections. The apparent protective effect of repellent was consistent across risk groups (village residents, forest dwellers and migrants) and villages, suggesting that repellent distributed by village health volunteers...
may be an effective intervention across a range of transmission intensity settings and populations. The study concluded that the large-scale distribution of repellent as part of malaria control and elimination programmes can be an effective public health tool to target residual malaria transmission in low transmission hard-to-reach areas of Myanmar and the GMS more broadly. Incorporating repellent into national strategies, particularly in areas where bed nets are less effective may contribute to the interruption of malaria transmission.

During the discussion, WHO noted that it is important to recognize that repellent use by individuals could lead to a positive public health impact. A public health impact does not require a community or mass effect and can arise through individual actions.

2.6.4 Safety, tolerability, and efficacy of triple artemisinin combination therapies: findings from Cambodia and Viet Nam

Dr Tom Peto and Dr James Callery presented MORU’s research on the efficacy of triple ACTs in Cambodia and Viet Nam. The study was a multi-centre, open-label randomized trial to assess the efficacy, safety and tolerability of the triple ACT artemether-lumefantrine + amodiaquine compared to the ACT artemether-lumefantrine in uncomplicated *P. falciparum* malaria in Cambodia and Viet Nam. A total of 600 patients from two sites in Cambodia and two sites in Viet Nam received either drug combination. The findings indicated that artemether-lumefantrine and artemether-lumefantrine + amodiaquine were both highly efficacious. The option of either as a first-line treatment needs to be further explored. The high efficacy of the ACT is reassuring for developing the triple ACT. A triple ACT is currently being developed, a co-packaged combination of artemether-lumefantrine + amodiaquine already exists.

2.6.5 The Regional Artemisinin-resistance Initiative’s RAI3E regional component operational research package

Mr Matteo Dembech, RAI Regional Steering Committee Secretariat, presented the RAI3E regional component operational research package for the upcoming funding allocation (2021–2023). Mr Dembech noted that the research priority topics with allocated funding are: (i) integration and sustainability, (ii) testing and radical cure for *P. vivax*, (iii) evaluating optimal tools for vector control, and (iv) the effectiveness of and alternatives to the 1-3-7 strategy in the GMS.

### 3. CONCLUSIONS AND RECOMMENDATIONS

3.1 Conclusions

Dr Tuseo thanked the GMS country participants, presenters, researchers, donors and partners for their comments and support. He summarized the main points from all the presentations and encouraged NMPs and partners to use the findings to continue to define optimal and sustainable approaches for malaria prevention, diagnosis and treatment and accelerate the transition from malaria control to elimination.

3.2 Recommendations

#### 3.2.1 Recommendation for Member States

NMPs are encouraged to strengthen or reactivate malaria operational research committees at the country level to define research priorities and establish an operational research agenda that addresses the dynamic challenges encountered on the path to malaria elimination.
## ANNEX 1

### Programme agenda

<table>
<thead>
<tr>
<th>Date and Time</th>
<th>Agenda</th>
<th>Speaker/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuesday, 24 November 2020</td>
<td>Opening Ceremony</td>
<td></td>
</tr>
<tr>
<td>13:00-13:10</td>
<td>Welcome address from WR Cambodia</td>
<td>Dr Li Ailan</td>
</tr>
<tr>
<td>13:10-13:15</td>
<td>Objectives of the meeting Nomination of chair, moderator and group photo</td>
<td>Dr Luciano Tuseo</td>
</tr>
<tr>
<td>13:15-13:30</td>
<td>An update on the development of malaria elimination guidelines</td>
<td>Dr Kimberly Ann Lindblade</td>
</tr>
<tr>
<td></td>
<td><strong>Session 1: Mass Drug Administration in the context of GMS countries, Target Drug Administration and Forest Malaria Prophylaxis</strong></td>
<td></td>
</tr>
<tr>
<td>13:30-14:00</td>
<td>Targeting high-risk populations with enhanced reactive case detection: a study to assess the effectiveness and feasibility for reducing <em>Plasmodium falciparum</em> and <em>Plasmodium vivax</em> malaria in Southern Lao PEOPLE’S DEMOCRATIC REPUBLIC and Thailand</td>
<td>University of California, San Francisco (UCSF) (Dr Timothy P Finn)</td>
</tr>
<tr>
<td>14:00-14:30</td>
<td>Minimizing the risk of malaria among forest goers in the Greater Mekong subregion: A randomized controlled trial to estimate the efficacy and feasibility of a forest malaria prophylaxis over one month</td>
<td>Mahidol-Oxford Tropical Medicine Research Unit (MORU) (Prof Richard Maude)</td>
</tr>
<tr>
<td>14:30-15:00</td>
<td>The impact of targeted malaria elimination with mass drug administrations on <em>Plasmodium falciparum</em> malaria in Southeast Asia: a cluster randomized trial</td>
<td>Mahidol-Oxford Tropical Medicine Research Unit (MORU) (Dr Lorenz von Seidlein)</td>
</tr>
<tr>
<td>15:00-15:15</td>
<td>Coffee/Tea Break (15mn)</td>
<td></td>
</tr>
<tr>
<td>15:15-15:45</td>
<td>Deployment of malaria elimination interventions in high risk military populations: challenges and new opportunities</td>
<td>Armed Forces Research Institute of Medical Sciences (AFRIMS) (Dr Mariusz Wojnarski)</td>
</tr>
<tr>
<td>15:45-16:15</td>
<td>Will ivermectin mass drug administration help eliminating residual malaria in Greater Mekong subregion</td>
<td>Armed Forces Research Institute of Medical Sciences (AFRIMS)/Faculty of Tropical Medicine (Dr Kevin Kobylinski)</td>
</tr>
<tr>
<td></td>
<td><strong>Session 2: Radical Cure for P. Vivax (Testing and Community Level Implementation)</strong></td>
<td></td>
</tr>
<tr>
<td>16:15-16:45</td>
<td>Effectiveness of novel approaches to radical cure with tafenoquine and primaquine</td>
<td>Menzies School of Health Research (Prof Ric Price)</td>
</tr>
<tr>
<td>16:45-17:00</td>
<td>Implementation and evaluation of a model of care of Glucose-6-Phosphate Dehydrogenase activity testing and primaquine for Plasmodium vivax radical cure in Cambodia and (VIGTARC study)</td>
<td>The Center for Health and Social Development (HSD) Cambodia/The London School of Hygiene &amp; Tropical Medicine (LSHTM) (Prof Shunmay Yeung)</td>
</tr>
<tr>
<td>Time</td>
<td>Session Content</td>
<td>Presenter(s)</td>
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</tr>
<tr>
<td>17:00-17:15</td>
<td>Reactive and proactive case detection for the elimination of malaria in Cambodia forest goers (PACES study)</td>
<td>The Center for Health and Social Development (HSD) Cambodia/The London School of Hygiene &amp; Tropical Medicine (LSHTM) (Prof Shunmay Yeung)</td>
</tr>
<tr>
<td>17:15-17:45</td>
<td>Utilizing existing tools for Plasmodium vivax elimination</td>
<td>Shoklo Malaria Research Unit (SMRU) (Dr Cindy Chu)</td>
</tr>
</tbody>
</table>

**Wednesday, 25 November 2020**

**Session 3: New Malaria Antivectorial Tool**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session Content</th>
<th>Presenter(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13:00-13:30</td>
<td>Assessing the relationship between long-lasting insecticidal net material and long-lasting insecticidal net usage in Myanmar and Cambodia</td>
<td>Population Services International (PSI) Myanmar (Dr Si Thu Thein)</td>
</tr>
<tr>
<td>13:30-14:00</td>
<td>Myanmar Private Sector Antimalarial Outlet Survey 2019</td>
<td>Population Services International (PSI) Myanmar (Dr Ye Kyaw Aung)</td>
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</tbody>
</table>

**Session 4: Health System Strengthening: Integration of Malaria Community Health Workers**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session Content</th>
<th>Presenter(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14:00-14:30</td>
<td>Optimal community-delivered malaria elimination models for the Greater Mekong subregion</td>
<td>Burnet Institute (Dr Win Han Oo)</td>
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</tbody>
</table>

**Session 5: Surveillance and Malaria Elimination**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session Content</th>
<th>Presenter(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14:30-15:00</td>
<td>Using highly-sensitive rapid diagnostic tests compared to control for reducing the health center catchment- and village-level prevalence and incidence of <em>Plasmodium falciparum</em> among village residents and mobile and migrant and other high-risk populations in Champsak Province, southern Lao People’s Democratic Republic</td>
<td>University of California, San Francisco (UCSF) (Dr Timothy P Finn)</td>
</tr>
<tr>
<td>15:00-15:15</td>
<td>Coffee/Tea Break (15mn)</td>
<td></td>
</tr>
<tr>
<td>15:15-15:45</td>
<td>Environment analysis and surveillance to improve malaria elimination strategies (EASIMES)</td>
<td>Shoklo Malaria Research Unit (SMRU) (Dr Florian Girond/ Dr Jordi Landier)</td>
</tr>
<tr>
<td>15:45-16:15</td>
<td>Effectiveness of repellent delivered by village health volunteers in Myanmar</td>
<td>Burnet Institute (Prof Freya Fokkes)</td>
</tr>
<tr>
<td>16:15-16:30</td>
<td>Safety, tolerability, and efficacy of Triple Artemisinin Combination Therapies: findings from Cambodia and Vietnam</td>
<td>Mahidol-Oxford Tropical Medicine Research Unit (MORU) (Dr Tom Peto/Dr James Callery)</td>
</tr>
<tr>
<td></td>
<td>The Regional Artemisinin-resistance Initiative’s RA13E regional component operational research package</td>
<td>Regional Steering Committee secretariat (Mr Matteo Demeche)</td>
</tr>
</tbody>
</table>

**Conclusion and Closing**

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<thead>
<tr>
<th>Time</th>
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</tr>
</thead>
<tbody>
<tr>
<td>16:30-16:50</td>
<td>Conclusions</td>
<td>Dr Luciano Tuseo (WHO)</td>
</tr>
<tr>
<td>16:50-17:00</td>
<td>Closing Remarks</td>
<td>Chair of the meeting</td>
</tr>
</tbody>
</table>
ANNEX 2

List of participants, temporary advisers, representatives, international partners and Secretariat

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