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

24 November 2021
Virtual meeting
SECOND FORUM ON OPERATIONAL RESEARCH IN THE CONTEXT
OF THE LAST MILE OF MALARIA ELIMINATION
IN THE GREATER MEKONG SUBREGION COUNTRIES

Convened by:

WORLD HEALTH ORGANIZATION REGIONAL
OFFICE FOR THE WESTERN PACIFIC

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NOTE

The views expressed in this report are those of the participants of the Second Forum on Operational Research in the Context of the Last Mile of Malaria Elimination in the 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 Second Forum on Operational Research in the Context of the Last Mile of Malaria Elimination in the Greater Mekong Subregion Countries on 24 November 2021.
<table>
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<tr>
<th>Acronym</th>
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<tr>
<td>CIME</td>
<td>community-delivered integrated malaria elimination</td>
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<tr>
<td>COVID-19</td>
<td>coronavirus disease 2019</td>
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<td>EASIMES</td>
<td>environment analysis and surveillance to improve malaria elimination strategies</td>
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<tr>
<td>G6PD</td>
<td>glucose-6-phosphate dehydrogenase</td>
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<td>GMS</td>
<td>Greater Mekong Subregion</td>
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<td>ICMV</td>
<td>integrated community malaria volunteers</td>
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<td>MME</td>
<td>Mekong Malaria Elimination</td>
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<td>PCR</td>
<td>polymerase chain reaction</td>
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<td>PQ</td>
<td>primaquine</td>
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<td>RDT</td>
<td>rapid diagnostic test</td>
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SUMMARY

On 24 November 2021, the World Health Organization (WHO) Mekong Malaria Elimination (MME) programme organized the virtual Second Forum on Operational Research in the Context of the Last Mile of Malaria Elimination in the Greater Mekong Subregion Countries with representatives from national malaria programmes, focal points from Greater Mekong Subregion (GMS) countries, as well as technical experts and partners. The operational research forum focused on how to: improve uptake and scale-up of interventions; cost-effectively implement combinations of interventions; preserve the effectiveness of interventions in the face of resistance; and measure the success and impact of interventions. The Forum continued discussions on optimal and sustainable approaches for malaria prevention, diagnosis and treatment, and ways to facilitate linkages across the GMS to promote greater coordination.

The key discussions of the meeting included:

- **Targeting silent *P. vivax* reservoirs:** Earlier studies from Cambodia indicate that despite the use of rapid diagnostic tests (RDTs) and microscopy, *Plasmodium vivax* reservoirs persist as patients are rarely symptomatic and subjects have low parasitaemia. Institut Pasteur du Cambodge conducted a cross-sectional study prior to an intervention based on a serology-oriented test and treat strategy that will be performed in 2022. Preliminary data from the study with polymerase chain reaction (PCR) tests indicated that there was a visible malaria reduction, but a *P. vivax* reservoir remained. Further studies using entomological approaches will indicate if the transmission system remains.

- **Piloting the *P. vivax* radical cure in Cambodia using G6PD RDTs/biosensors and primaquine:** A study by the Center for Health and Social Development (HSD), the London School of Hygiene & Tropical Medicine (LSHTM) and Cambodia’s National Center for Parasitology, Entomology and Malaria Control’s (CNM) aimed to implement and evaluate a new model of care for glucose-6-phosphate dehydrogenase (G6PD) testing and primaquine (PQ) for the radical cure of *P. vivax*. Under this study, patients with RDT-confirmed *P. vivax* infections were referred to local health centres for a G6PD test. According to the test result, treatment with PQ was initiated, with follow-up through village malaria workers. Findings indicate that the *P. vivax* radical cure using the health facility–community care model is feasible and highly acceptable and should be scaled up nationwide.

- **G6PD point-of-care testing to support radical cure:** Two studies were conducted in Viet Nam and the Lao People’s Democratic Republic to assess G6PD testing and primaquine administration as part of malaria case management. In the Lao People’s Democratic Republic, the study was conducted by the Center for Malaria, Parasitology, and Entomology (CMPE), University of California, San Francisco (UCSF), and PATH, and in Viet Nam it was conducted by the National Institute of Malariaology, Parasitology, and Entomology (NIMPE) and PATH. The studies reinforce the need for robust supervision and on-the-spot retraining to ensure high user competency with new test devices and treatment guidelines is maintained. Full results from the Lao People’s Democratic Republic and Viet Nam studies are forthcoming.

- **Community-delivered models in the Lao People’s Democratic Republic and Myanmar:** Burnet Institute has led a mixed-methods multi-country operational research project to identify community-delivered malaria elimination model(s) that is acceptable, operational, pragmatic, and cost-effective across GMS countries. The community-delivered integrated malaria elimination (CIME) model is developed integrating voices from community members and leaders, and local and health stakeholders, and ongoing field-testing in Myanmar. It expands the role of integrated community malaria volunteers (ICMVs) to cover interventions for malaria elimination as well as other common health problems such as dengue, tuberculosis, RDT-negative febrile illness and childhood diarrhoea. Health stakeholders and community members...
in the Lao People’s Democratic Republic have also been consulted and proposed an integrated community-delivered health-care model similar to the CIME model in Myanmar.

- **Chemoprophylaxis in the GMS:** Mahidol-Oxford Tropical Medicine Research Unit (MORU) conducted a study on the efficacy and feasibility of a forest malaria prophylaxis intervention in Cambodia, the Lao People’s Democratic Republic and Thailand. The findings from the trial in Cambodia indicate chemoprophylaxis with artemether-lumefantrine was acceptable, well-tolerated, and reduced malaria infections. In-depth interviews with key stakeholders on the feasibility of prophylaxis in Cambodia, the Lao People’s Democratic Republic and Thailand indicate that the strategies must be context specific and need to be tailored to the local situation. Where feasible, malaria prophylaxis among high-risk groups such as forest goers is a promising additional tool for malaria elimination in the GMS.

- **EASIMES (environment analysis and surveillance to improve malaria elimination strategy):** A research project of Shoklo Malaria Research Unit in eastern Myanmar aims to improve the understanding of environmental conditions that influence malaria transmission in the forested environments. The Malaria Environmental Surveillance System is live, allowing users to optimize approaches for active surveillance, allocate resources and target interventions based on the data generated on the forest environment and malaria.
1. INTRODUCTION

1.1 Background

In 2015, the World Health Organization (WHO), national malaria programmes, and partners launched the WHO Strategy for Malaria Elimination in the Greater Mekong Subregion (2015–2030). The plan outlined a commitment to eliminate Plasmodium falciparum malaria from the Greater Mekong Subregion (GMS) by 2025 and all species of human malaria by 2030. Following a steep decline in malaria cases, the GMS countries recently agreed to move the P. falciparum elimination target forward to 2023. Priority actions are targeted to areas where multidrug-resistant malaria has taken root. 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 agreed to work together with relevant entities to ensure that all research efforts are nationally coordinated and 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. To provide timely results to inform policy-making and malaria elimination efforts, WHO’s Mekong Malaria Elimination (MME) programme organized the Second Forum on Operational Research in the Context of the Last Mile of Malaria Elimination in the Greater Mekong Subregion Countries on 24 November 2021. The Forum continued efforts to facilitate linkages across the GMS and discuss pertinent research findings related to malaria prevention, diagnosis and treatment.

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:
   a. improving the radical cure of P. vivax malaria,
   b. integrating surveillance for malaria elimination into health systems, and
   c. adapting tools and addressing barriers to prevention, diagnosis and treatment.

2) to accelerate the transition from malaria control to elimination and beyond by identifying good practices to:
   a. accelerate malaria elimination, and
   b. prevent reestablishment and maintain zero malaria cases.

2. PROCEEDINGS

2.1 Opening session of day 1

Dr Li Ailan, WHO Representative, Cambodia, delivered the welcome address to the participants. She emphasized that operational research on malaria continues to play a critical role in solving ongoing implementation problems and can respond to the rapidly changing malaria epidemiology of the GMS. She also encouraged participants to consider the ways operational research can be applied in the differing local contexts to improve the sustainability of existing interventions. Following this, Dr Luciano Tuseo, Coordinator of the MME programme, provided a briefing of the meeting objectives. This was followed by the nomination of Professor Maxine Whittaker, Co-Director WHO Collaborating Centre of Vector Borne and Neglected Tropical Diseases, as the chair of the meeting.
2.2 Session 1: Optimal and sustainable approaches for malaria prevention, diagnosis and treatment

2.2.1 Targeting silent P. vivax reservoirs

Dr Benoit Witkowski presented Institut Pasteur du Cambodge’s study on targeting silent P. vivax reservoirs in Cambodia. Institut Pasteur du Cambodge conducted a cross-sectional study prior to an intervention based on a serology-oriented test and treat strategy that will be performed in 2022. The cross-sectional study covered more than 2000 individuals in 16 villages from Kaeo Sima district, Mondulkiri Province. The study indicated that the majority of P. vivax malaria infections were among males as men are more likely to work in forest-based occupations. Despite the use of rapid diagnostic tests (RDT) and microscopy, P. vivax reservoirs persist as patients are rarely symptomatic and subjects have low parasitaemia. Microscopy and RDT are poorly sensitive for these cases. Therefore, alternative approaches to microscopy and RDTs are needed to target this reservoir. In 2019, a cohort study was launched with 900 individuals from Kaeo Sima who were screened with polymerase chain reaction (PCR) tests. This study is looking at how the asymptomatic/symptomatic status of the individual evolves. Preliminary data from the PCR tests indicated that there was a visible malaria reduction but a P. vivax reservoir remained. Further studies will indicate if the transmission system remains. This will include data collection to reflect the acceptability of serological testing and treatment within the population. In addition, an entomological component will determine the Anopholes population and parasite carriage rate in surrounding forests and plantations before and after the implementation of activities.

During the discussion, Dr Witkowski noted that the PCR data indicated that villages that were close to or surrounded by forests showed the highest prevalence of P. vivax cases. Despite a decrease in recent years, data from 2020 still show a prevalence of malaria (mainly P. vivax) of approximately 15–25% in the study villages.

2.2.2 Vivax G6PD Testing and Radical Cure Project in Cambodia (VIGTARC)

Dr Soy Ty, The Center for Health and Social Development (HSD) presented an ongoing study to develop and implement scalable models of care for patients with P. vivax involving referral from the community, G6PD testing by health-care workers, treatment with primaquine (PQ) and follow-up in the community. The study is a joint collaboration between HSD, the London School of Hygiene & Tropical Medicine (LSHTM) and Cambodia’s National Center for Parasitology, Entomology and Malaria Control (CNM). Under this study, health centre staff and village malaria workers performed malaria diagnosis testing using malaria RDTs, biosensor analysers and provide first-line malaria treatment with artesunate-mefloquine. Patients detected by village malaria workers were referred to health centres for a G6PD Test and PQ for P. vivax radical cure. According to the test result, treatment with PQ was initiated, with follow-up through village malaria workers. Village malaria workers visited patients with a normal G6PD status at home on days three, seven and 14 for a 14-day PQ regimen. G6PD-deficient patients were visited on weeks three, four, five, six, seven and eight for the eight-week PQ regimen.

The study began in July 2019 and ended in June 2021. Between July 2019 and December 2020, 100% of the 551 patients with a normal G6PD status completed the 14-day PQ radical cure. In addition, 94% of the 51 male patients with a G6PD deficiency completed the eight-week PQ radical cure. In total, 8% of patients had second episodes after the PQ radical cure. Focus group discussions with patients indicated that they felt minimal side-effects and were confident that PQ can cure P. vivax but a 14-day regimen is long. Village malaria workers reported that many patients had previously sought P. vivax treatment. After the P. vivax radical cure they did not come back for treatment. Performing directly observed treatment was considered beneficial.

Findings indicate that the P. vivax radical cure using the health facility–community care model is feasible and highly acceptable and should be scaled up nationwide. PQ was generally very well-tolerated, and, with community support, high levels of adherence to the 14-day regime were achieved.
2.2.3 Integrating G6PD point-of-care testing into malaria case management to support radical cure: an assessment of health worker skills and knowledge in the Lao People’s Democratic Republic and Viet Nam

Ms Huyen Nguyen, PATH, presented two studies from Viet Nam and the Lao People’s Democratic Republic to assess the operational feasibility and safety of G6PD testing and PQ administration as part of malaria case management. The studies also aimed to assess the perceptions of health-care workers and patients on G6PD testing. They also assessed the capacity of health-care workers to integrate quality-assured quantitative G6PD testing and safe radical cure into routine case management.

In Viet Nam, the study involved the National Institute of Malaria, Parasitology, and Entomology (NIMPE) and PATH. In the Lao People’s Democratic Republic, the study was conducted by the Center for Malaria, Parasitology, and Entomology (CMPE), University of California, San Francisco (UCSF), and PATH. District hospital laboratory and health centre staff at 23 facilities in malaria-endemic regions of the Lao People’s Democratic Republic and Viet Nam were trained in the use of a point-of-care G6PD biosensor-based diagnostic. A multiple-choice test and an observational component were used to assess user knowledge and competency, where users completed the diagnostic workflow and interpreted the test result using control reagents under supervision.

In the Lao People’s Democratic Republic, assessment scores improved between the baseline and midline assessments, particularly for the observational assessment. A refresher training and supervision visits were conducted in response to the baseline scores. Conversely, in Viet Nam, health worker scores were higher after training than at the midline assessment. This may be due to health workers having limited opportunity or cause to practise using the test, as there was a low number of *P. vivax* patients treated during the study.

Baseline G6PD assessments were conducted for each health centre staff with previous training. At most health facilities, one staff member was much stronger than others. District hospital staff had an easier time conducting the tests and quality control as would be expected.

Interim results from Viet Nam indicate 96.8% of the 44 trained health workers were certified as proficient in the use of G6PD tests after the initial training and 74.1% passed the standardized competency assessment at the midline evaluation. All *P. vivax* patients enrolled in the study received G6PD tests, and 83.3% of *P. vivax* cases received appropriate radical cure treatment. The 16.7% of *P. vivax* cases that did not receive the appropriate radical cure treatment was due to patient refusal to go to a higher-level facility for an eight-week course of PQ after being diagnosed as G6PD deficient. Results from the Lao People’s Democratic Republic are forthcoming.

The studies reinforce the need for robust supervision and on-the-spot retraining to ensure high user competency with new test devices and treatment guidelines is maintained. Developing novel supportive materials for health workers such as video tutorials aided training during coronavirus disease 2019 (COVID-19) movement and travel restrictions. WhatsApp and Zalo groups with district supervisory and study staff quickly resolved questions and provided instant support.

During the discussion, Ms Huyen Nguyen noted that PATH developed two job aids for health workers in Viet Nam. The first job aid outlined the steps to run the G6PD tests and second job aid covered quality control for the tests. Dr Timothy Finn confirmed that similar job aids were developed for the Lao People’s Democratic Republic. Once health workers built their competency to perform tests, there were few issues in compliance. However, running the controls resulted in some compliance issues as it a more complex process.

2.2.4 Evaluation of community-delivered models in the Lao People’s Democratic Republic and Myanmar

Dr Win Han Oo presented the Burnet Institute’s research on optimal community-delivered malaria elimination models for the GMS. The Burnet Institute has led a mixed-methods multi-country operational research project to identify community-delivered malaria elimination model(s) that is acceptable, operational, pragmatic and cost-effective across GMS countries. Different integrated
community-delivered models have been developed, piloted and evaluated globally. In the GMS, the integrated community malaria volunteer (ICMV) model is the current standard of care in Myanmar and the volunteer malaria worker and village health volunteer models are used in other GMS countries. While the malaria volunteers mainly focus on control and elimination of malaria, the ICMVs 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 in Myanmar together with the findings from a comprehensive systematic review and meta-analysis of community-delivered models led to the adaptation and development of the community-delivered integrated malaria elimination (CIME) model, which 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 case and foci investigations, larval source management, as well as referral and prevention services for dengue, tuberculosis, childhood diarrhoea and RDT-negative fevers. Field-testing of the CIME model is ongoing using a stepped-wedge cluster randomized controlled trial covering 74 villages in Myanmar in 2021 and 2022.

Health stakeholders and community members in the Lao People’s Democratic Republic have proposed an integrated community-delivered health-care model that treats malaria and addresses other health issues such as dengue, diarrhoea, influenza, skin infections and tuberculosis, which would be similar to the CIME model developed for Myanmar.

2.3 Session 2: Accelerating the transition from malaria control to elimination and beyond by identifying good practices

2.3.1 Chemoprophylaxis in Cambodia, the Lao People’s Democratic Republic and Thailand

Dr Richard Maude, Mahidol-Oxford Tropical Medicine Research Unit (MORU), presented a study on the efficacy and feasibility of a forest malaria prophylaxis intervention in Cambodia, the Lao People’s Democratic Republic and Thailand. The study aimed 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 planning to stay overnight in the forest from 15 villages with malaria cases in Steung Treng. The study was unblinded, individually randomized and controlled, and 1480 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 also mapped participants’ travel in the forest to identify potential transmission sites. Prior to starting the study, community engagement was delivered through community meetings, and later through one-on-one meetings (due to COVID-19 restrictions). The findings from the trial in Cambodia indicate chemoprophylaxis with artemether-lumefantrine was acceptable, well-tolerated, and reduced the number of subsequent \textit{Plasmodium} infections by approximately sixfold over a three-month period. Where feasible, malaria prophylaxis among high-risk groups such as forest goers is a promising additional tool for malaria elimination in the GMS.

In-depth interviews were also 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 interviews indicate that the strategies must be context specific and need to be tailored to the local situation. Prophylaxis was perceived as a viable option for control in Cambodia when combine with other existing interventions and village malaria...
workers are potential providers. Respondents from Thailand perceived it as an unnecessary option when there are already successful strategies for elimination. There were major concerns about non-adherence where drug resistance is a threat. Interviewees from the Lao People’s Democratic Republic perceived prophylaxis as a viable option but noted that more evidence is needed on efficacy and how it could be implemented in the country context.

During the discussion, Dr Maude noted that artemether-lumefantrine is a good candidate for chemoprophylaxis as long as it is not being used the first-line drug (as this creates a risk of resistance). The target population received compensation for any costs incurred for travel. Participants were provided biscuits along with the drugs in order to ensure absorption.

2.3.2 EASIMES (Environment Analysis and Surveillance to improve Malaria Elimination Strategy)

Dr Florian Girond, Institut de Recherche pour le Développement (IRD), presented Shoklo Malaria Research Unit’s (SMRU) research project in eastern Myanmar aims to improve the understanding of environmental conditions that influence malaria transmission in the forested environments. The project developed the Malaria Environmental Surveillance System. This web-based data platform aims to reinforce the microstratification and active surveillance tools used by national malaria programmes by allowing users to optimize approaches for active surveillance, allocate resources and target interventions based on the data generated on the forest environment and malaria. The system includes an accurate land-use/land-cover database and regional early warning system based on environmental factors. The land-use/land-cover 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 Malaria Environmental Surveillance System is fully operational and used by partners and the national malaria programme in Myanmar. In addition, surveillance tools will be expanded to cover COVID-19, tuberculosis and HIV. This will allow health providers to track in real time the location of patients, their numbers and to model the impact of connectivity between villages, on the distribution of the diseases.

3. CONCLUSIONS

3.1 Concluding remarks

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 national malaria programmes 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.
## Annex 1. Programme agenda

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<tr>
<td>Wednesday, 24 November 2021</td>
<td>Chair: Dr Maxine Whittaker, WHO Collaborating Centre for Vector Borne and Neglected Tropical Diseases</td>
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<tr>
<td><strong>13:00-13:20</strong></td>
<td>Welcome address by WHO Cambodia Representative</td>
<td>Dr Li Ailan (WHO)</td>
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<td>Objectives of the meeting and nomination of chair</td>
<td>Dr Luciano Tuseo (WHO MME)</td>
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<td><strong>Session 1: Optimal and sustainable approaches for malaria prevention, diagnosis and treatment</strong></td>
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<td><strong>13:20-13:55</strong></td>
<td>Targeting silent <em>P. vivax</em> reservoirs</td>
<td>Dr Benoit Witkowski, Institut Pasteur du Cambodge</td>
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<td><strong>13:55-14:30</strong></td>
<td>Piloting the <em>P. vivax</em> radical cure in Cambodia using G6PD RDTs and primaquine</td>
<td>Dr Soy Ty (HSD)</td>
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<td><strong>14:30-15:20</strong></td>
<td>Integrating G6PD point-of-care testing into malaria case management to support radical cure: an assessment of health worker skills and knowledge in Lao People’s Democratic Republic and Vietnam</td>
<td>Huyen Nguyen (PATH) and Dr Timothy Finn (UCSF)</td>
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<td><strong>15:20-15:30</strong></td>
<td>Group photo and coffee/tea break (on your own)</td>
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<td><strong>15:30-16:05</strong></td>
<td>Evaluation of community delivered models in Lao People’s Democratic Republic and Myanmar</td>
<td>Dr Win Han Oo, Burnet Institute</td>
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<td><strong>Session 2: Accelerating the transition from malaria control to elimination and beyond by identifying good practices</strong></td>
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<td><strong>16:05-16:40</strong></td>
<td>Chemoprophylaxis in Cambodia, Lao People’s Democratic Republic and Thailand</td>
<td>Dr Richard Maude (MORU)</td>
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<td><strong>16:40 – 17:05</strong></td>
<td>EASIMES (Environment Analysis and Surveillance to improve Malaria Elimination Strategy)</td>
<td>Dr Florian Girond (IRD)</td>
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<td><strong>Conclusion</strong></td>
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<td><strong>17:05 – 17:20</strong></td>
<td>Conclusions</td>
<td>Dr Luciano Tuseo (WHO MME)</td>
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<td>Closing Remarks</td>
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Annex 2. List of participants, observers and Secretariat

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