Meeting Report

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

28–29 October 2019

Yangon, Myanmar

World Health Organization
Western Pacific Region

WORLD HEALTH ORGANIZATION

REGIONAL OFFICE FOR THE WESTERN PACIFIC

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Convened by:

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NOTE

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

This report has been prepared by the World Health Organization Regional Office for the Western Pacific for Member States in the Region and for those who participated in the Seventh Meeting of the Greater Mekong Subregion (GMS) Therapeutic Efficacy Studies (TES) Network in Yangon, Myanmar from 28 to 29 October 2019.

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Keywords:

Antimalarials – therapeutic use / Malaria – drug therapy, prevention and control / Mekong valley / Regional health planning

ABBREVIATIONS

ACPR	adequate clinical and parasitological response
ACT	artemisinin-based combination therapy
AL	artemether + lumefantrine
ASAQ	artesunate + amodiaquine
ASMQ	artesunate + mefloquine
ASPY	artesunate + pyronaridine
CQ	chloroquine
DHA-PPQ	dihydroartemisinin + piperaquine
G6PD	glucose-6-phosphate dehydrogenase
GMS	Greater Mekong Subregion
iDES	integrated drug efficacy surveillance
K13	Kelch 13
MME	Mekong Malaria Elimination
NTG	national treatment guidelines
PCR	polymerase chain reaction
Pfpm2-3	*Plasmodium falciparum* plasmepsin 2-3
PPQ	piperaquine
PQ	primaquine
TES	therapeutic efficacy studies
WHO	World Health Organization

SUMMARY

The Seventh Meeting of the Greater Mekong Subregion (GMS) Therapeutic Efficacy Studies (TES) Network was convened in Yangon, Myanmar, on 28–29 October 2019. Participants from five countries of the GMS – Cambodia, the Lao People's Democratic Republic, Myanmar, Thailand and Viet Nam – attended the meeting. The WHO Regional Office of South-East Asia, the WHO Regional Office for the Western Pacific and the WHO Global Malaria Programme organized the two-day meeting to support countries in reviewing the implementation of TES and integrated drug efficacy surveillance (iDES) activities, discussing results from the past 12 months and planning TES and iDES activities for the next two years.

In the last decade, *Plasmodium falciparum* parasites in the GMS have developed partial resistance to artemisinin, as well as resistance to some artemisinin-based combination therapy (ACT) partner drugs. This resistance has made it imperative for GMS countries to reach their shared goals of eliminating *P. falciparum* malaria by 2025 and of all human species of malaria by 2030. With evidence suggesting no major increase in artemisinin partial resistance in the past year, the GMS countries are presented with a critical window to eliminate *P. falciparum*.

Updating each country's national treatment guidelines with effective antimalarials is crucial to achieving elimination. National programmes, with support from WHO and partners, monitor antimalarial drug efficacy through TES and iDES. Cambodia and the Lao People's Democratic Republic are currently piloting iDES, while Thailand has expanded iDES and used results to drive policy change.

Results from TES and iDES are supplemented by data from genetic monitoring, such as information on molecular markers such as Kelch 13 (K13). During the meeting, participants discussed the latest data from TES, iDES and genetic markers. On the final day, GMS countries shared their plans and budgets for TES and iDES implementation over the next two years.

The objectives of the meeting were:

1) to review and discuss implementation and results of the recent TES and iDES in the GMS countries and discuss related implementation of other 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 malaria drug resistance; and
3) to develop GMS and country workplans and budgets for TES and iDES implementation and monitoring for 2020–2021.

Conclusions

Overview of GMS malaria elimination: In 2018 and the first half of 2019, there has been significant progress towards *P. falciparum* elimination in the GMS. Between January and September 2019, approximately 89% of malaria cases were *P. vivax* or mixed cases. Malaria is mostly concentrated in remote areas, where the disease disproportionately affects forest goers.

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

Drug efficacy: TES is the gold standard for monitoring drug efficacy to inform treatment policy. In Myanmar, data suggest that artemether + lumefantrine (AL), artesunate + mefloquine (ASMQ), artesunate + pyronaridine (ASPY) and dihydroartemisinin + piperaquine (DHA-PPQ) are highly efficacious. In Cambodia, ASMQ and ASPY are also efficacious. For the Lao People's Democratic Republic, ASPY and ASMQ are efficacious, while the efficacy of AL is under review. High failure rates for DHA-PPQ are reported in one province in the Lao People's Democratic Republic and Viet Nam. In Viet Nam, data suggest that ASPY is efficacious. For Thailand, ASMQ and DHA-PPQ are

efficacious, except in two provinces where DHA-PPQ demonstrates higher failure rates. Chloroquine for *P. vivax* is also failing in one province of Thailand.

Integrated drug efficacy surveillance: As the number of malaria cases decline, sample size for TES becomes increasingly difficult to achieve. In elimination settings, the system for collection of drug efficacy can be shifted from sentinel sites to an iDES system. Cambodia and the Lao People's Democratic Republic are piloting iDES. Thailand has expanded iDES and used iDES data to drive policy change in two provinces.

National treatment guidelines: ACTs are available and have been tested in GMS countries, but some countries still need to shift from their second-line treatment of quinine. Low-dose primaquine for treatment of *P. falciparum* is included in all national treatment guidelines but not fully operationalized in some countries.

Quality control monitoring: Quality control monitoring helps to identify gaps and challenges for improvement in TES and iDES implementation. In the past year, there have been significant improvements in all GMS countries. One challenge is the recent procurement of laboratory equipment that did not meet minimum quality standards.

Genetic markers: Molecular analysis is in accordance with high efficacy of ASMQ in Cambodia, but this status is susceptible to evolving. Close monitoring therefore remains crucial for Cambodia.

Recommendations

Member States are encouraged to consider the following:

1) Continue monitoring the quality of TES implementation based on the WHO quality control checklist.
2) Continue efforts to strengthen quality assurance for microscopy and molecular assays for achieving elimination.
3) Review the results of TES within countries; consider switching the first-line drug, if the first-line drug is no longer effective nationally or subnationally.
4) Encourage the use of alternative ACT as second-line treatment, rather than quinine.
5) National malaria control programmes should work with country national regulatory authorities to identify bottlenecks and accelerate the registration process of antimalarials, as well as post-marketing surveillance for quality and safety.

WHO is requested to consider the following:

1) Share the latest TES template with all GMS countries.
2) Continue providing support for countries moving into elimination settings, particularly as they transition to iDES, including the finalization of the iDES protocol.
3) Support countries to review and revise national treatment guidelines based on available TES data and other information.
4) Support the operationalization of revised national treatment guidelines with partners.

1. INTRODUCTION

1.1 Background

Protecting the efficacy of antimalarial drugs is essential to curing malaria patients and eliminating the disease from the Greater Mekong Subregion (GMS) by 2030. GMS countries have made substantial progress. Between 2012 and 2018, the reported number of malaria cases fell by 74% and the number of malaria deaths fell by 95%. As the number of cases continues to decline, countries will need to shift towards integrated drug efficacy surveillance (iDES), through which routine monitoring of drug efficacy becomes part of the surveillance system.

WHO has been hosting meetings of the GMS Therapeutic Efficacy Studies (TES) Network since 2008 to support countries in reviewing drug efficacy data and developing country-specific plans for efficacy monitoring. GMS countries continue to use TES as the gold standard for monitoring drug efficacy. Thailand has expanded its iDES system, and Cambodia and the Lao People's Democratic Republic are piloting iDES. Data on genetic markers for resistance (e.g. Kelch 13) are also used to enhance the monitoring of multidrug resistance in the Subregion.

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

There are still remaining challenges in the Subregion. The full implementation of national treatment guidelines (NTGs) has yet to be operationalized in all GMS countries. This includes replacing ineffective first-line treatments, implementing a single low dose of primaquine (PQ) for *Plasmodium falciparum* and implementing *P. vivax* radical cure. There are also issues with drug registration in some countries, which prevents immediate utilization of alternative artemisinin-based combination therapies (ACTs) if first-line drugs are found to be no longer efficacious.

1.2 Objectives

The objectives of the meeting were:

1) to review and discuss implementation and results of the recent TES and iDES in the GMS countries and discuss related implementation of other control activities;
2) to discuss the role and results of K13, the molecular marker for tracking artemisinin