Meeting Report

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

27–28 September 2018

Luang Prabang, Lao People's Democratic Republic

World Health Organization
Western Pacific Region

WORLD HEALTH ORGANIZATION

REGIONAL OFFICE FOR THE WESTERN PACIFIC

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Convened by:

WORLD HEALTH ORGANIZATION
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NOTE

The views expressed in this report are those of the participants of the Sixth 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 Sixth Meeting of the Greater Mekong Subregion (GMS) Therapeutic Efficacy Studies (TES) Network in Luang Prabang, Lao People's Democratic Republic from 27 to 28 September 2018.

CONTENTS

Keywords:
Drug resistance / Malaria / Regional health planning / Asia, Southeastern

ABBREVIATIONS

ACPR	adequate clinical and parasitological response
ACT	artemisinin-based combination therapy
AL	artemether + lumefantrine
AM	artemether
AS	artesunate
ASAQ	artesunate + amodiaquine
ASMQ	artesunate + mefloquine
ASPY	artesunate + pyronaridine
BVBD	Bureau of Vector Borne Diseases
CMPE	Centre for Malaria, Parasitology and Entomology
CQ	chloroquine
DBS	dried blood spots
DHA-PPQ	dihydroartemisinin + piperaquine
G6PD	glucose-6-phosphate dehydrogenase
GMS	Greater Mekong Subregion
iDES	integrated drug efficacy surveillance
IPC	Institut Pasteur du Cambodge
K13	Kelch 13
MME	Mekong Malaria Elimination
MQ	mefloquine
NTG	National Treatment Guidelines
PCR	polymerase chain reaction
Pf	*Plasmodium falciparum*
Pfpm2-3	Pf plasmepsin 2-3
PPQ	piperaquine
PQ	primaquine
Pv	*Plasmodium vivax*
PYR	pyronaridine tetraphosphate
QA	quality assurance
QC	quality control
RDT	rapid diagnostic test
TES	therapeutic efficacy studies
WHO	World Health Organization

SUMMARY

The Sixth Meeting of the Greater Mekong Subregion (GMS) Therapeutic Efficacy Studies (TES) Network was convened in Luang Prabang, Lao People's Democratic Republic, from 27 to 28 September 2018. Organized by the WHO regional offices for South-East Asia and the Western Pacific, it brought together participants from the six GMS countries: Cambodia, China, Lao People's Democratic Republic, Myanmar, Thailand and Viet Nam. The TES Network Meeting supports countries in monitoring progress and reviewing TES results as well as in planning and implementing future TES and integrated drug efficacy surveillance (iDES) activities over the next two years.

The emergence of multidrug-resistant malaria parasites in the GMS necessitates strengthening monitoring efforts. The drug resistance of antimalarial medicines is monitored by conducting TES. These aim to inform policy-makers about the efficacy of currently used drugs for evidence-based national treatment policy change, and to identify alternative artemisinin-based combination therapies (ACTs) for revision of national treatment guidelines, as necessary.

Surveillance for antimalarial drug efficacy through TES in burden reduction areas or iDES in pre-elimination areas is important to identify early deterioration of antimalarial drugs and update national treatment regimens promptly. Data from molecular markers, such as Kelch 13 (K13), also help to monitor drug resistance in the GMS.

During the TES Network Meeting, participants reviewed and discussed results from TES and iDES as well as molecular data for K13 and other markers. On the final day, country participants developed plans and budgets for TES and iDES implementation and monitoring for the next biennium.

The objectives of the meeting were:

- 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;
- 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
- to develop GMS and country work plans and budgets for TES and iDES implementation and monitoring for 2019–2020.

Conclusions

Overview of GMS malaria elimination: GMS countries have achieved substantial progress towards malaria elimination, but significant transmission remains in some parts of Cambodia, the Lao People's Democratic Republic, Myanmar and Viet Nam. The remaining challenges include: 1) sustainable financing; 2) project implementation in the remaining endemic areas and partnership coordination, 3) monitoring and addressing multidrug resistance, and 4) strengthening surveillance.

Status of artemisinin resistance: Artemisinin partial resistance alone does not affect the overall efficacy of ACTs if the partner drug remains effective. ACTs fail when parasites are resistant to the partner drug or to both artemisinin and the partner drug. In such cases, countries need to consider changing the first-line ACT.

TES results: Study results indicate that artemisinin partial resistance (presence of validated K13 mutants) and resistance to multiple partner drugs primarily affect the eastern part of the GMS (east of a vertical line drawn across Bangkok). In Cambodia, its adjacent provinces in the Lao People's

Democratic Republic, Viet Nam and Thailand showed high failure rates for dihydroartemisinin-piperaquine (DHA-PPQ), which is the first-line drug in Viet Nam and Thailand. In the Lao People's Democratic Republic, the efficacy of artemether-lumefantrine (AL) as a first-line drug is also declining. In Cambodia, artesunate–mefloquine (ASMQ) and artesunate-pyronaridine (ASPY) are efficacious, while the other countries are currently monitoring their efficacy. Based on the absence of the *Plasmodium falciparum* multidrug resistance 1 gene (pfmdr1) copy number prevalence, ASMQ should be efficacious in all countries listed. Myanmar data showed high efficacy rates (more than 90% for AL, DHA-PPQ, ASMQ and ASPY).

Quality control monitoring: Quality control monitoring is important to ensure the quality of TES and iDES implementation, with a focus on the clinical and laboratory (microscopy and polymerase chain reaction (PCR) assays) outcomes, data validation, field coordination to facilitate patient enrolment, and regular on-site supervision to address field challenges. This monitoring allows for reliable data that can drive drug policy review/changes in a country.

National treatment guidelines: The GMS countries have different ACTs as first-line treatments. Most countries have quinine for seven days as a second-line treatment. However, the seven-day treatment with quinine is difficult to implement. All countries have low-dose primaquine (PQ) as a supplementary treatment for *P. falciparum*, but it is not yet operationalized in some countries. Training at health centres and in the community on the use and safety of low-dose PQ is crucial. All countries have PQ (14 days or 8 weeks) for radical cure of *P. vivax* in their national treatment guidelines. However, the implementation of this policy has been slow. In addition to the selection of drugs, other issues are critical to accelerate the elimination of malaria, such as universal access to prevention and treatment, functional community treatment networks, drug management (adequate stocks of ACTs and rapid diagnostic tests or RDTs in health centres and village malaria worker networks), and quality assurance of ACTs. Although the use of triple combination therapy (e.g. DHA-PPQ plus mefloquine) has been evaluated in some countries, the additional benefit (over ASMQ) is unclear if DHA-PPQ is no longer effective.

Genetic markers: Results from molecular marker analyses in Cambodia, the Lao People's Democratic Republic, Myanmar and Viet Nam are largely in line with TES findings. Cambodia and Viet Nam showed high resistance rates against artemisinin and piperaquine, although Cambodia officially decided to stop the use of DHA-PPQ around three years ago. There are no or very limited signs of resistance against mefloquine and PYR. Results from the Lao People's Democratic Republic did not demonstrate signs of resistance for the samples investigated. Of note, there were no K13 mutants detected in samples collected during the 2017 outbreak in Savannakhet. Results from Myanmar showed some resistance to artemisinin, but not to partner drugs.

Transition to iDES: As countries approach elimination and malaria transmission declines, strengthened surveillance systems can be used to collect and analyse data on drug efficacy. Through iDES, countries can transition from using a sentinel surveillance system to relying on efficacy data collected via the routine surveillance system. Thailand started piloting the feasibility of iDES in eight provinces in 2017; China is planning a pilot for iDES for imported *P. falciparum* and *P. vivax* cases.

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 microscopy quality assurance for TES and elimination purposes.
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 sub-nationally.
4) Identify alternative ACT as second-line treatment, based on the TES results, and discontinue the use of quinine.
5) Accelerate the roll-out of glucose-6-phosphate dehydrogenase (G6PD) point-of-care (POC) tests (or other measures such as close monitoring) to enable the radical cure of *P. vivax* with primaquine.
6) Accelerate the registration process of all ACTs and test alternative ACTs in the TES.
7) Review and consider implementation of relevant recommendations from the Meeting on Addressing Urgent Issues Pertaining to Antimalarial Drug Management to Facilitate Accelerated Elimination of Malaria from the GMS Countries of the Western Pacific Region (Phnom Penh, Cambodia, 26–28 February 2018).

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) Review and revise national treatment guidelines based on available TES data and other information.
4) Support the full operationalization of revised national treatment guidelines with national programmes and partners, including low single dose of primaquine for *P. falciparum* infections.