Meeting Report

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

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

World Health Organization
Western Pacific Region

WORLD HEALTH ORGANIZATION REGIONAL OFFICE FOR SOUTH EAST ASIA AND 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 Fifth Meeting of the Greater Mekong Subregion (GMS) Therapeutic Efficacy Studies (TES) Network and do not necessarily reflect the policies of the World Health Organization.

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

CONTENTS

Keywords:

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

ABBREVIATIONS

ACPR	adequate clinical and parasitological response
ACT	artemisinin-based combination therapy
AL	artemether + lumefantrine (Coartem™)
AM	artemether
AS	artesunate
AS-AQ	artesunate + amodiaquine
AS+SP	artesunate + sulfadoxine-pyrimethamine
ASMQ	artesunate + mefloquine
AS-PYR	artesunate + pyronaridine tetraphospate (Pyramax™)
BVBD	Bureau of Vector Borne Diseases
CNM	National Center for Parasitology, Entomology and Malaria
CQ	chloroquine
DHA-PIP	dihydroartemisinin + piperaquine
ERAR	Emergency Response to Artemisinin Resistance
G6PD	glucose-6-phosphate dehydrogenase
iDES	integrated drug efficacy surveillance
IPC	Institut Pasteur du Cambodge
K13	Kelch 13
MQ	mefloquine
MME	Mekong Malaria Elimination
NIMPE	National Institute of Malariology, Parasitology and Entomology
NIMR	National Institute for Malaria Research
NIRTH	National Institute for Research in Tribal Health
NMCP	National Malaria Control Programme
NTG	National Treatment Guidelines
PCR	polymerase chain reaction
Pf	*Plasmodium falciparum*
Pfpm2-3	Pf plasmepsin 2-3
Pm	*Plasmodium malariae*
Po	*Plasmodium ovale*
Pv	*Plasmodium vivax*
PMI	President’s Malaria Initiative
PQ	primaquine
QA	quality assurance
QC	quality control
RDT	rapid diagnostic test
TES	therapeutic efficacy studies
USAID	United States Agency for International Development
WHO	World Health Organization

SUMMARY

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

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

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

The objectives of the meeting were:

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

Conclusions

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

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

implications for ensuring that appropriate treatment is given are significant, given the changes in national treatment guidelines.

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

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

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

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

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

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

Recommendations for Member States

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

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

3) Alternative ACT regimens need to be tested before declining efficacy becomes apparent.

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

Recommendations for WHO

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

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

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

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

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