Report of the workshop to review and plan therapeutic efficacy studies to monitor *P. falciparum* and *P. vivax* resistance to anti-malarial drugs in the Greater Mekong Sub-region

Mandalay, Myanmar, September 30 - October 2, 2009

World Health Organization
Regional Office for South-East Asia

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Acknowledgements

The workshop to review and plan therapeutic efficacy studies (TES) to monitor *P. falciparum* and *P. vivax* resistance to anti-malarial drugs in the Greater Mekong Sub-region was organized in collaboration with the Global Malaria Programme in WHO Headquarters, the WHO Regional Offices for South-East Asia and the Western Pacific and coordinated by the WHO Mekong Malaria Programme Office in Bangkok. The workshop was hosted by the Myanmar National Malaria Programme and the WHO Myanmar country office.

The organizers of the workshop thank all facilitators for their technical inputs and assistance to ensure monitoring of TES country plans in the Mekong countries. The organizers also thank all representatives from Mekong countries for their involvement in the proper and timely implementation of TES country proposals planned in 2007 and their continued commitment and interest in the *in vivo* TES MMP network.

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Executive Summary

The Greater Mekong Sub-region (GMS) is known as the global epicentre of *P. falciparum* resistance to antimalarial drugs. All six countries of the Mekong region are promoting the use of artemisinin-based combination therapies (ACTs) as first-line drug therapy to manage uncomplicated malaria cases or have used artemisinin monotherapies during the last 15 years. The *in vivo* TES MMP Network coordinated by WHO aims to monitor the therapeutic efficacy of these first-line therapies by promoting the use of a single standardized protocol across Mekong countries and by accurately checking the quality of data generated by studies carried out in agreed upon sentinel sites. The TES Network is also increasingly looking at *P. vivax* resistance to chloroquine which is of growing concern in the GMS.

A WHO MMP informal consultation in January 2007 in Cambodia acknowledged the decreased sensitivity of *P. falciparum* to ACTs on the Cambodia-Thailand border triggering immediate in-depth research studies to confirm that worrisome situation. A key recommendation from the informal consultation was to strengthen the *in vivo* MMP TES Network to carefully monitor the therapeutic efficacy of anti-malaria drugs across the GMS by using agreed upon in vivo standardized protocols. An informal consultation was organized in Phuket Thailand in September 2007 with representatives and principal investigators from malaria control programmes of Cambodia, China, Lao PDR, Myanmar, Thailand and Viet Nam as well as partners. Participants agreed to use the updated WHO TES protocol and related case management guidelines to monitor drug resistance in the GMS. Countries drafted their country plans and two-year budget to conduct *in vivo* TES in selected sentinel sites to monitor *P. falciparum* and *P. vivax* efficacy to first-line antimalarial drugs in 2008 and 2009 (e.g. seven-day artemisinin monotherapy in China and Viet Nam). The efficacy of antimalarial drugs was studied in patients against clinical symptoms and parasite counts during at least 28-days follow-up by adhering to strict standardized entry criteria and cross-checking strict quality data analysis procedures. Re-infections or recrudescence were determined through the systematic use of polymerase chain reaction (PCR) techniques, including genotyping and use of molecular markers for resistance. It was also envisioned to strengthen the MMP molecular laboratory network in the region. During the two-year implementation period, TES training workshops

targeting field staff and country visits to assess TES performance against planning have been conducted in all countries.

The *Mekong Malaria Programme in vivo Therapeutic Efficacy Network* has intensified its support to 32 sentinel sites in six GMS countries since September 2007. Preliminary results were presented by PIs in Mandalay, Myanmar in September 2009. Longer parasite clearance time and decreasing efficacy rate (ACPR) of ACTs have been observed in Kawthaung on the south-eastern part of Myanmar bordering Thailand (province of Ranong) where ACPR (using AS+M) has been also declining since 2006. Preliminary results also show a longer parasite clearance time (beyond day 3) to AS7 monotherapy in Dehong, Yunnan province of China bordering Myanmar, and in Binh Phuoc province in southern Viet Nam bordering Cambodia (province of Snoul). Such worrying but yet preliminary results have to be further validated. For example, slide validation (species and counting) especially on day 3 and day of failure is perceived as an urgent step to confirm worrying results. All countries have expressed their need for refresher training courses on malaria microscopy and parasite counting especially when identification and measurement of parasites at day 1-3 are considered critical endpoints to monitor therapeutic failure of ACT and/or AS7.

Since artemisinin/ACT resistance does not seem to be only confined on the Cambodia-Thailand border but might have extended to the Myanmar-Thailand, China-Myanmar and Cambodia-Viet Nam borders, additional *in vivo* studies with 7-day artemisinin monotherapies including PK of As and molecular fingerprinting of parasite genomes to track artemisinin resistance (gene flow) circulating around the region are planned in 2010-2011 in the six countries. Molecular biology tools and markers are becoming increasingly crucial to be identified / used through whatever samples collected in the GMS. Also noted during the workshop was the increasing complexity to recruit malaria cases through a single sentinel site channel against required sample size in most of Mekong countries. New multi-district/sentinel sites approaches will be discussed and piloted to address that situation.

Acronyms

ACPR	adequate clinical and parasitological response
ACT	artemisinin-based combination therapy
ACTMalaria	Asian Collaborative Training Network for Malaria
ARC3	Artemisinin Resistance Confirmation, Characterization, Containment Project
AL	Artemether – Lumefantrine
AMO	Amodiaquine
AMT	Artemisinin monotherapy
AP	Atovaquone-Proguanil (Malarone©)
AS	Artesunate
AS7	7-day Artesunate treatment
AS + M	Artesunate-Mefloquine (co-packaged in Cambodia, loose tablets in Thailand)
BCC	Behavioural Change Communication
BMGF	Bill and Melinda Gates Foundation
BVBD	Bureau of Vector-Borne Diseases, Thailand
CQ	Chloroquine
CDC	US Center for Disease Control and Prevention (Atlanta)
CNM	Cambodian National Center for Parasitology, Entomology and Malaria Control
DHA	Dihydroartemisinin
DHAPIP	Dihydroartemisinin-piperaquine (co-formulated)
DMA	Department of Medical Research (Myanmar)
EC	Ethical Committee
ETF	Early Treatment Failure

GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMS	Greater Mekong Sub-region
GFATM	Global Fund to fight AIDS, TB and Malaria
IC50	50% Inhibitory Concentration
ICF	Informed Consent Form
IRB	Institutional Review Board
Lao PDR	Lao People's Democratic Republic
LCF	Late Clinical Failure
LFU	Loss to follow-up
LLIN	Long-lasting Insecticidal Nets
LPF	Late Parasitological Failure
NIMPE	National Institute of Malariology, Parasitology and Entomology, Viet Nam
NIPD	National Institute of Parasitic Diseases, China
NMCP	National Malaria Control Programme
M&E	Monitoring and Evaluation
MMP	Mekong Malaria Programme
MoH	Ministry of Health
MORU	Mahidol Oxford Tropical Medicine Research Unit
PCR	Polymerase Chain Reaction
PCT	Parasite clearance time
PI	Principal Investigator
PIP	Piperaquine
Pf	*Plasmodium falciparum*
Pfmdr1	*Plasmodium falciparum multidrug resistance 1 gene*

PfSERCA	*Plasmodium falciparum sarcoplasmic endoplasmic reticulum Ca2+ ATPase*
PRR	Parasite Reduction Ratio
Pv	Plasmodium vivax
RDM-A	Regional Development Mission – Asia (USAID)
RDT	Rapid Diagnostic Test
SEARO	WHO Regional Office for South-East Asia
SOP	Standard Operating Procedure
SP	Sulfadoxine-pyrimethamine
TES	Therapeutic Efficacy Study
TRG	Technical Reference Group
QA	Quality Assurance
QC	Quality Control
USAID	United Stated Agency for International Development
USP	United States Pharmacopeia
WWARN	Worldwide Antimalarial Resistance Network
WHO	World Health Organization
WHO-TDR	Special Programme for Research and Training in Tropical Diseases
WPRO	WHO Regional Office for the Western Pacific
WPRO-ERC	WHO Regional Office for the Western Pacific Ethics Review Committee
WTH	Withdrawal of patients

1. Introduction

1.1 Background

The Greater Mekong Sub-region (GMS) is well known as the global epicentre of *P. falciparum* resistance to antimalarial drugs. It is in this region (which comprises Cambodia, China's Yunnan province, Lao PDR, Myanmar, Thailand and Viet Nam), that resistance emerged to chloroquine, sulfadoxine-pyrimethamine and mefloquine, before spreading to other parts of the world. All six countries of the Mekong region have introduced artemisinin-based combination therapies (ACTs), which are currently the only effective therapies against multidrug-resistant malaria strains. Likewise, there is also growing concern of *P. vivax* resistance to chloroquine in the GMS.

In January 2007, the World Health Organization (WHO) Mekong Malaria Programme (MMP) held an informal consultation in Phnom Penh, Cambodia, to take stock of knowledge pertaining to multi-drug resistant malaria in Cambodia and Thailand[1]. Results from various studies concluded the evidence of decreased sensitivity of falciparum infections to ACTs on the Cambodia-Thailand border urging in-depth research studies to validate such observations. A key recommendation from the meeting was also to strengthen the MMP network to monitor antimalarial drug resistance by using and supporting standardized methodologies in sentinel sites across the GMS.

As a result, an informal consultation with representatives from all Mekong countries and partners was organized by the WHO Mekong Malaria Programme (MMP) in Phuket, Thailand, on 3-5 September 2007[2]. Participants included representatives and principal investigators from malaria control programmes of the six countries in the GMS (Cambodia, China, Lao People's Democratic Republic, Myanmar, Thailand and Viet Nam), WHO, the United States Agency for International Development (USAID), the Asian Collaborative Training Network for Malaria

[1] WHO South-East Asia Region and Western Pacific Region. *Containment of malaria multi-drug resistance on the Cambodia-Thailand border: Report of an informal consultation.* Phnom Penh, Cambodia, 29-30 January 2007, SEA-MAL-246

[2] WHO South-East Asia Region and Western Pacific Region: *Monitoring Resistance of P. falciparum and P. vivax to Antimalarial Drugs in the Greater Mekong Sub-region*, Phuket, Thailand, 3-5 September 2007, SEA-MAL-250

(ACTMalaria), United States Pharmacopeia (USP) and Kenan Institute Asia. WHO provided an update on recent protocols and guidelines to monitor therapeutic efficacy of anti-malarial drugs. National malaria programmes then developed, budgeted and presented their 2008-9 draft country plans to conduct *in vivo* TES *[P. falciparum* and *P. vivax]* to first-line anti-malarial drugs in 2008 and 2009 in selected sentinel sites. Participants agreed on methodologies and the guideline to be used throughout the GMS and to be technically and financially supported by WHO. It was also planned to consolidate laboratory networking across the Greater Mekong Subregion to assess and standardize molecular biology techniques (SOPs) and to genotype and use molecular markers for resistance. Therapeutic efficacy study (TES) workshops have been conducted in all countries and country visits for monitoring TES performance have taken place in all countries throughout the implementation period.

The first year results of the studies in parallel to other studies have confirmed artemisinin treatment failure and slower PCT mainly at the Cambodia-Thailand border. At the consultation in Phuket, it was also planned to perform studies to determine if therapeutic failure of artemisinin/ACT is found in other locations in the region. Important multi-country initiatives have then started in the GMS since September 2007. One of them is the two-year bi-country containment project of artemisinin resistance on the Cambodia-Thailand border led by WHO with financial support from the Bill and Melinda Gates Foundation (BMGF).

The WHO-Mekong Malaria Programme, based in Bangkok, is managing the Mekong *in vivo* TES network in articulation with the WHO South-East Asia and Western Pacific regional offices. The overarching goal of the TES network is to contribute to update, in a timely manner, national anti-malaria drug policies in the GMS countries. The TES network is expected also to document the geographical extension of *P. falciparum* resistance to artemisinin-based combinations (ACT) and artesunate monotherapies and *P. vivax* resistance to chloroquine in the GMS.

1.2 Objectives of the workshop

The workshop had the intention to achieve the following objectives:

(1) To review implementation of WHO TES protocol in all GMS countries against the WHO protocol and initial planning,

(2) To review and consolidate results from TES in the GMS,

(3) To develop regional and country workplans and budget of TES for the next two-year period (2010-2011),

(4) To clarify relationship and harmonization of WHO-supported *in vivo* TES with new related initiatives in the GMS.

1.3 Participants

Representatives and Principal Investigators (PIs) from national malaria programmes participated in the workshop (except from China) as well as donors (USAID, BMGF and PMI), MMP partners (ACTMalaria, US-CDC and Malaria Consortium) and observers from WWARN and the newly established MM surveillance Network. The list of participants is in Annex 5.

1.4 Opening Session

The workshop was opened by Dr Win Myint, Director-General, Department of Health, Ministry of Health. Myanmar. The key messages highlighted were that antimalarial drug resistance has emerged as one of the greatest challenges hindering the progress of malaria control today. Drug resistance has been implicated in the spread of malaria to new areas and re-emergence of malaria in areas where the disease had been eradicated. It has also played a significant role in the occurrence and severity of epidemics in some parts of the world. Population movement has introduced resistant parasites to areas previously free of drug resistance.

Sensitivity of the antimalarial drugs is critical for an effective treatment strategy. Therefore, Myanmar, like other countries in the region, supports the need for therapeutic efficacy surveillance, PCR analyses and pharmacokinetic studies. If artemisinin resistance is to be contained it must happen through a concerted effort between countries, agencies, partners and donors.

As resistance to one or more antimalarial drugs occurs more frequently, malaria control programmes and other concerned institutions need to be able to evaluate antimalarial drug efficacy in a way that provides timely, relevant, reliable, and understandable information. Updated information on artemisinin-resistant *P. falciparum* malaria should be exchanged and discussed very thoroughly among all Member States.

Dr Leonard Ortega, Acting WHO Representative to Myanmar, welcomed all participants and said that Member States have made significant progress in the monitoring of therapeutic efficacy of various antimalarial drugs using the WHO *in vivo* protocol. However, there are challenges related to the interpretation and actual implementation of the protocol, ensuring quality of drugs to be tested, quality of data collection, and others. This workshop will enable the participants to update themselves on what has been done so far, share lessons learned and plan for the next two years.

Dr Ortega appreciated that more partners are engaged and interested in the work done in malaria control in the Greater Mekong Sub-region and welcomed the representatives from USAID, US-CDC, Bill and Melinda Gates Foundation, Malaria Consortium, ACTMalaria, WWARN project and the molecular marker network. Dr Ortega also thanked the Ministry of Health, Myanmar, for support in holding the workshop and acknowledging the financial assistance from USAID through WHO for this important activity.

1.5 Appointment of Chairpersons and rapporteurs

Day 1: The chairperson and co-chair were Dr Than Win, Deputy Director (Malaria), Disease Control, Department of Health, Myanmar and Dr Samlane Pomphida, Director of the Centre for Malariology, Parasitology and Entomology, Ministry of Health, Lao PDR, respectively.

Day 2: The chairperson and co-chair were Dr Khin Lin, Director, DMR Upper Myanmar and Dr Khung Sim, Vice Director of National Centre for Malariology, Parasitology and Entomology, Ministry of Health, Cambodia, respectively.

Day 3: The chairperson and co-chair were Dr Ye Htut, Director of DMR Lower Myanmar and Dr Wichai Satimai, Director of Bureau of Vector-Borne Disease, Department of Disease Control, Ministry of Health, Thailand, respectively.

Dr Maria Dorina Bustos and Ms Charlotte Rasmussen were appointed as rapporteurs.

1.6 Proceedings

The proceedings included a technical presentation by Dr P. Ringwald, updates on the containment project on the Thai-Cambodian border by Dr E. Christophel and Dr C. Delacollette, an overview of the main challenges to implement TES in the GMS by Dr D. Bustos and an introduction to the ethical considerations and procedures to follow when carrying out health research activities involving human subjects by Dr E. Christophel. Furthermore, Dr P. Guerin & Dr C. Plowe introduced the WWARN project and gave an overview of the future perspectives of the molecular markers surveillance network. Principal investigators from each country (except China) presented their two-year preliminary results from TES *(P. falciparum* and *P. vivax)* conducted in 2008 and partially in 2009. Subsequently, the countries developed and presented in plenary their 2010-11 country TES plans. The agenda of the three-day workshop is in Annex 4.

2. Presentations

2.1 General presentations

Monitoring P. falciparum and P. vivax resistance to antimalarial drugs: a global overview and progress made as part of the ARC3 project

Presenter: Dr Pascal Ringwald

Dr Ringwald (WHO-HQ) gave a presentation on the progress and success in the monitoring of *P. falciparum* and *P. vivax* resistance to antimalarial drugs. He reminded participants about WHO's expected role to monitor the therapeutic efficacy of anti-malarial drugs as follows:

- To develop the template protocol,
- To assure the standardization of data entry and data analysis methodology,
- To advocate for and secure funding when available, and give training on the protocol and on microscopy,

- To provide free of charge quality antimalarial medicines to be used as part of TES,
- To cross-check quality of results,
- To report on the results.

As the result of TES conducted worldwide, 77 endemic countries have updated their national anti-malarial drug policy further implemented in many low income countries thanks to the GFATM. Last year's consolidated results from the *in vivo* TES MMP network show that the proportion of patients who are still parasitaemic on day 3 (72 hours after the intake of the first dose) is an essential indicator which is measuring the parasite clearance time (PCT is expected to be less than 48-hours with ACTs). Such indicators, in addition to the traditional ones as per WHO protocol (28 days or 42 days), provide an early warning intelligence of potential therapeutic failure of tested artemisinin monotherapies and ACTs. Last year's results from ARC3[3] show that *in vivo* phenotype does not correlate to standard *in vitro* assays. Thus, there is no correlation between artesunate IC50s and PRR at 24 h and 48 h, and the proportion of patients still parasitaemic on day 1, day 2 or day 3 and PCT in general. Furthermore, the lack of *in vitro* correlation may be due to the use of wrong technical tools / techniques. There was no correlation as well between a number of different mutations (*pfSERCA* or mtDNA mutations -*coxIII* gene) or pfmdr1 copy number and clinical outcomes.

Containment of malaria multi-drug resistance on the Cambodia-Thailand border: progress made

Presenter: Dr Eva Christophel

Dr Christophel (WHO-WPRO) presented a brief overview of the strategy currently implemented in "hot- spot" areas where artemisinin treatment failure has been documented. The overarching goal of the strategy in these areas is to contain resistant parasites by removing selection pressure and reducing and ultimately eliminating *P. falciparum* malaria. The development

[3] WHO: Minutes of the ARC3 investigators' meeting, 28-29 September 2009, Siam City Hotel, Bangkok, Thailand

of the strategy has been through an intensive consultative process involving country programmes, international experts, interested partners and WHO.

The main components of the strategy are:

(1) To eliminate tolerant parasites by detecting the majority of malaria cases in target areas and ensuring effective treatment and gametocyte clearance,

(2) To prevent use of artemisinin-based monotherapies (AMT), fake drugs and inappropriate treatment in the private sector,

(3) To prevent transmission of tolerant /resistant parasites by mosquito control and personal protection,

(4) To limit the spread of tolerant/resistant parasites by targeting mobile populations,

(5) To support containment of tolerant/resistant parasites through comprehensive / harmonized BCC,

(6) Community mobilization and advocacy, to ensure strategies applied are evidence-based,

(7) To apply an effective management system, including surveillance, monitoring and evaluation to enable rapid and accurate implementation of the strategy.

The main financial contributor to the containment project is the Bill and Melinda Gates Foundation (BMGF). Progress to date from January 2009 is as follows: to set up the bi-country organizational structure, to finalize large-scale procurement, to plan and distribute LLINs, to hold three technical workshops, to initiate operational research and to set up an M&E – surveillance system. A steering committee has been established (International Task Force) with six international experts, representatives from programmes, partners, donors and from WHO. In addition to ITF, two national task forces (Cambodia and Thailand) are functioning to coordinate field work and update national experts and the international community on progress made including consolidation of national reports. Among the main priorities is the involvement of the private sector in order to slow down the trade / traffic of artemisinin monotherapies. Furthermore, the focus will be on increasing access to health services by migrants and the cross-border mobile population and to scale up surveillance including mapping and follow-up of patients still positive at Day3. Intensifying and consolidating

cross-border cooperation is also perceived as an essential task e.g. to ensure follow-up of cross- border patients.

The discussion after the presentation focused on the need to use experience gained from current containment efforts in Cambodia and Thailand to set up similar active approaches in neighboring countries where a similar worrying situation is documented like in the eastern states of Myanmar. An important concern is how to address the use of (substandard) monotherapies by private sector providers, how to improve national regulations and enforce laws.

Operational challenges in implementing TES in the GMS

Presenter: Dr Maria Dorina Bustos

As per definition from the WHO TRG guidelines (WHO WPRO handbook, April 2009), therapeutic efficacy studies fall under the category of human biomedical research with interventions done over and above routine activities generating new knowledge for action. All TES protocols must then be submitted to the WHO TRG. The most common problem relates to late submission of incomplete protocols and informed consent forms without clearance from the national ethics committee, thus incurring further delays in the final approval and release of budget from WHO.

Other technical challenges, as mentioned individually by Mekong countries, are as follows:

- Sentinel site selection and timing of study affecting sample size and recruitment;
- Slide validation and parasite counting procedures by "qualified" microscopists;
- Proper PCR and pharmacokinetic (PK) sample collection and storage;
- Treatment drugs - external/internal QC analysis of drugs used; section on correct dose (no. of tabs) by body weight has to be computed for and double checked;
- Clinical trial registration per country which has to be performed by MOH-NMCP (Website: http//www.ANZCTR.org.au);

- Strict protocol adherence and quality of data generated (to be cross checked)
- Technical report writing.

Other administrative challenges as observed during the monitoring visits are:

- Lack of TES supervision and monitoring by principal investigator (PI)
    - Additional dedicated time by PIs to carefully scrutinize protocol to be submitted to the TRG
    - Multiple responsibilities given to PIs by programme managers
- Re-training of TES field implementers and microscopists are needed
- Timely release of budget/logistics by WHO
- GCP/GLP procedures to be followed up.

The WHO TES protocol is not a simple easy-to-implement protocol to be handled by NMCPs as a programmatic routine activity only. The overall concern relates to quality control procedures in general which are not routinely observed by national programmes (as compared to research institutions). This can be achieved, however, under NMCP management with further practice and constant quality supervision over time by PIs. There is recognition by Mekong countries that non-expert microscopists and other provincial microscopists assigned to the sentinel sites need further proficiency assessment and re-training sessions to ensure QA in malaria diagnosis and parasite counting.

A question was raised on the quality and ID labels of the filter paper blood spots collected in the field by all six countries since 2008. SOPs for blood collection and storage of PCR and CQ pharmacokinetic filter paper samples are in place. A major issue is where to process all these samples and from which funding sources e.g. for molecular and pharmacokinetic investigations. As mentioned by Dr Ringwald, PIs are facing the same situation elsewhere in the world with overstocks of PCR filter papers waiting to be processed. The recent USAID grant to Prof Chris Plowe at the University of Maryland, a new partner in the Mekong Malaria Programme,

can contribute to process, analyze and cross-check PCR samples with national agreement. However, some countries like China do not allow any biological samples to be processed outside the country. This is a situation where in-country technical collaboration and laboratory capability strengthening has to be provided.

Health research involving human research subjects: ethical considerations and procedures to follow

Presenter: Dr Eva Maria Christophel

It is mandatory to have an ethical review of biomedical research proposals involving human subjects to protect potential participants in the research, and also take into account potential risks and benefits for the community in which the research will be carried out. A review is required by international ethical standards governing research involving human participants, as well as by local law in many countries. In international cooperative research, review may also be required by the laws/regulations of the country/organization which funds/sponsors the research. The Nuremberg Code (1947), the Declaration of Helsinki (six versions since 1964, latest 2008) and the Council of International Organizations of Medical Sciences (CIOMS): International Ethical Guidelines for Biomedical Research Involving Human Subjects (1993, 2002) embody guidelines based on the principle of respect for research subjects and obligation of researchers/sponsors to offer best proven care to trial participants during the research project, and also addresses issues such as compensation and access to post-trial care for participants.

National or institutional ethics committees exist in most GMS countries, but not all, with a required translation into national language. WHO has an institutional ethics review committee: WPRO-ERC (Ethics Review Committee), SEARO and HQ-ERC.

Issues which were admonished by the WPRO-ERC in the 2009 TES proposals:

- National ethical review committee approval
    - Either missing or inappropriate (signed by PI)

- The protocol and Informed Consent Forms *(ICF)*
  - TES template not adapted to national situation (e.g. consent form titles)
  - Assent form and consent form for pregnancy test missing
  - Content was not harmonized with the requirements of a linked *in vitro* proposal
- Others:
  - PI signed proposals also on behalf of the "institutional endorsement" (should be Ministry of Health)
  - WHO was named as a "sponsor"
  - Optional tests (Annex 7) not specified
  - Separate data collection forms for *Pf* and *Pv* monitoring were requested.

One of the issues was the extension of 2008 proposals which were not able to be completed in 2008 and for which protocol amendment and extension have been granted to shorten national IRB and WPRO-ERC time.

The concept of the generic *in vivo* TES protocol is to have an agreed-upon protocol satisfying national programmes and researchers which can be widely used in different situations and different countries. The purpose is to help NMCPs and research groups to use a standardized protocol allowing quality data to be generated and managed to produce recognized quality results to be compared over time and space. However, it also means that there are parts of the protocol that might not be relevant in specific situations. In countries without an ethics committee, a letter from the MOH stating that "*there is no ethical concern on this protocol*" is still requested by WHO. WHO is not considered as a sponsor but the NMCP-MOH does and shoulders legal liability. A two-year protocol is not acceptable to the WHO/HQ ERC since an annual report is mandatory to the ERC for an expedited review and approval. Along the same line, there is a need to strengthen national ERCs. This can be done through specific linkages with ACTMalaria, WHO-TDR and US-CDC. Even non-WHO-funded TES protocols have to go through the WHO ERC when technical assistance and data management quality control is provided by WHO consultants. Another issue raised by the WHO-ERC relates to the drugs being tested whether they are registered in the country or not or when used in another dosage as

compared to WHO guidelines. In such a situation, the national ERC requires the "investigational drug" approval from the local drug regulatory agency, and likewise submission to the WHO ERC.

WWARN project and molecular marker network: objectives and perspectives

Presenters: Dr Christopher Plowe and Dr Philippe Guerin

Dr Christopher Plowe (University of Maryland) and Dr Philippe Guerin (University of Oxford) gave an overview of the work of WWARN (Worldwide Antimalarial Resistance Network hosted by the University of Oxford). The mission of WWARN is to provide comprehensive, up to date, quality-assured information on antimalarial drug resistance to guide the control and elimination of malaria. To achieve this, WWARN has established collaboration with WHO[4] with the goal of standardizing data formats and thereby allowing meta-analysis from diverse studies. WWARN also promotes sharing and mapping of data. This will assist in providing spatio-temporal evidence on drug efficacy and thus be a good evidence base for policy makers from a regional and global perspective. The platform and the entry point to WWARN will be the WWARN website (http://www.wwarn.org). One of the essential modules of WWARN is a module to monitor molecular markers. A goal of the molecular markers module is to develop a global database for molecular markers to accelerate the identification and validation of markers to monitor ACT resistance. WWARN furthermore aims to improve the use of molecular markers as a public health tool because it is a simple, scalable and inexpensive way to perform surveillance and to guide local, national and regional antimalarial policy. The network will promote and support molecular marker testing in underrepresented and "sensitive" regions like the GMS. USAID / RDM-A has recently awarded a contract to the University of Maryland / WWARN Molecular Module to support national and regional laboratories to perform molecular surveillance of potential drug resistant malaria strains in the GMS. Part of the MMP Molecular Network tasks will be to perform a need assessment in each country looking at capacity building, lab equipment,

[4] Memorandum of understanding between WHO and the Chancellor, Masters and Scholars of the University of Oxford ("*the WHO/Oxford MoU*")

quality lab procedures (SOPs), exchange of materials, identification of potential markers to artemisinin resistance and tracking resistance gene flow in the GMS.

For researchers and programmes wishing to share their raw data through special agreements, this can be done either by the researchers themselves uploading their data on the website or through WHO by giving special permission to WHO (special MoU to be agreed upon and signed by both parties) to upload and share their data. Uploaded country data through WHO will have to be preliminarily validated by WHO. Data will remain the property of researchers who will ultimately give permission to share data. Once validated data are uploaded /posted on the WWARN website, specific designed tools will help to analyze, visualize and report on posted data. In 2009, WWARN will open an office in Bangkok (Mahidol) that will assist and support interested researchers in the region.

After the presentation, concerns were raised by researchers about the extent to which their data would need to be cleaned and validated before the data could be uploaded. It was, however, pointed out that WWARN would be ready with any assistance needed in cleaning and validating the data. The *"curator"* will work together with the PI on how to use, define variables and validate data. Researchers also pointed out that sharing of data would need the support of policy makers. It was underlined by the presenters that even after the data are uploaded, the data belong to the country and would only be shared if permission is given through appropriate channels. Partners pointed out that data have to be shared not only at the national or regional level but also globally since policy makers worldwide look at the Greater Mekong Sub-region as a "hotspot" for drug resistance and generating information for evidence-based policy making.

2.2 Country presentations

Figures 1 and 2 show the study sites and antimalarial drugs tested in the six Mekong countries. There are 34 sentinel sites in the six countries, with either one or two drugs tested against *P. falciparum* or *P. vivax* or both species, in 2008 and 2009 respectively. All countries have adhered to the standard WHO 28-day or 42-day therapeutic efficacy protocol and used the WHO recommended Excel programme for data management. The

sample size was calculated according to the malaria prevalence and expected rates of failure in the selected sites with a sample size of at least 50 patients per site. However, this sample was difficult to reach in some sentinel sites due to the very low malaria transmission situation resulting from aggressive control measures.

Figure 1. ***From the consultation in Phuket in September 2007, this map shows locations where TES were planned to be performed in 2008 with identification in brackets of anti-malarial drugs to be tested. TES were not performed in locations mentioned in italics but carried out in 2009 instead.***

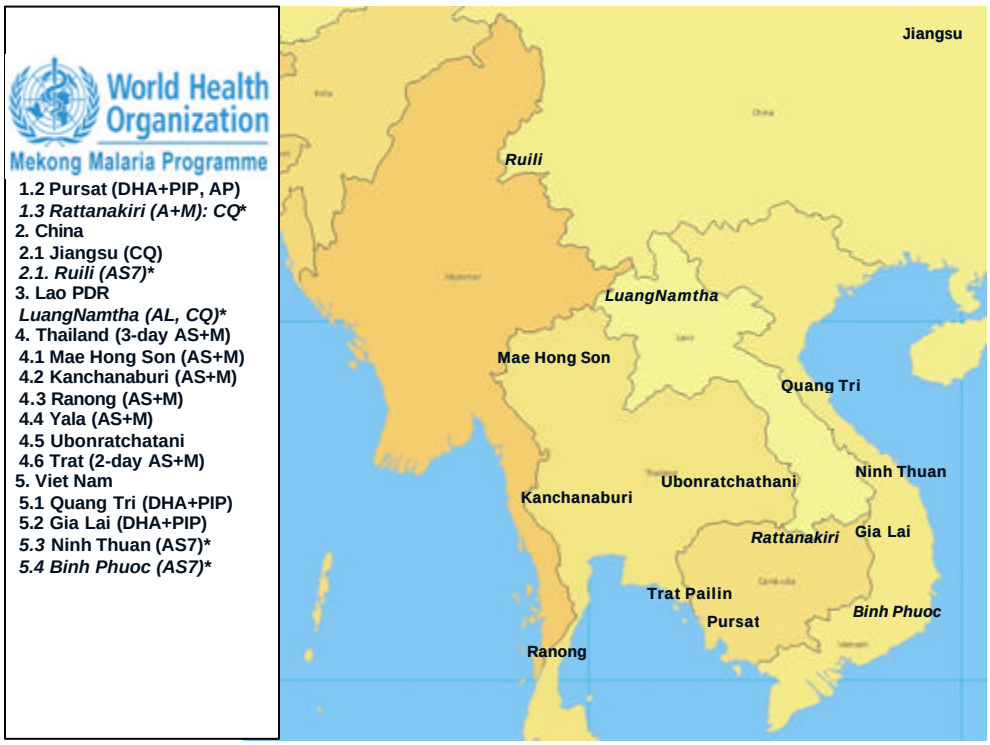
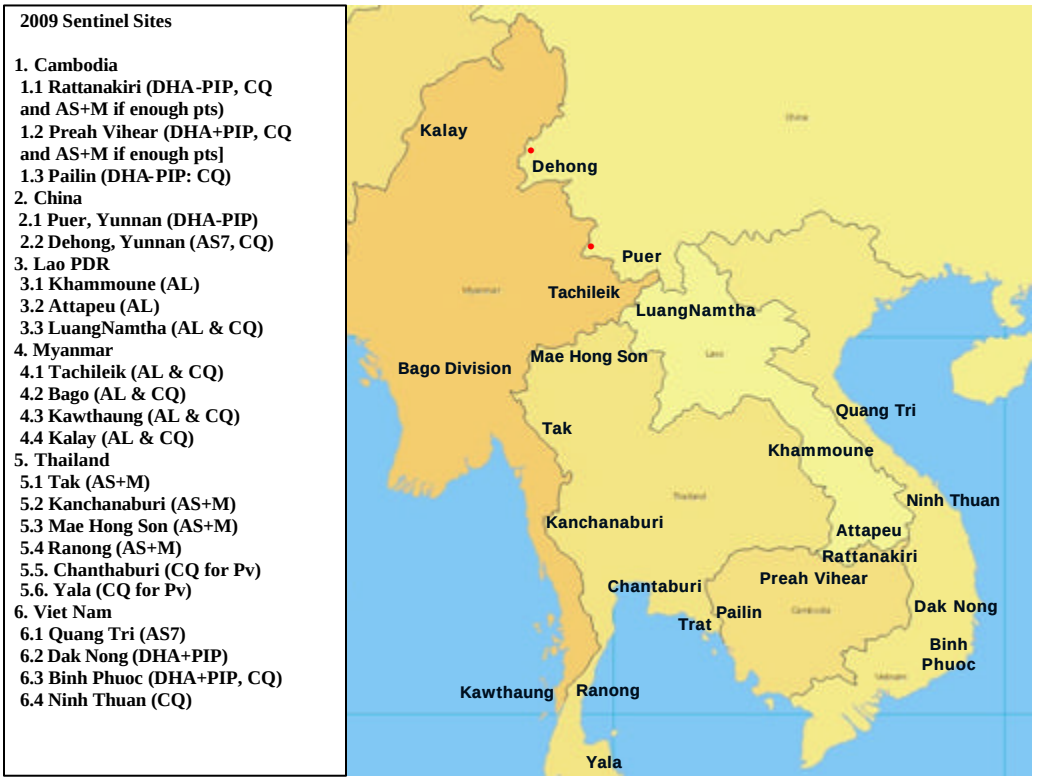


Figure 2. ***TES performed in 2009 in the GMS***



Cambodia

Dr Leang Rithea, from CNM Phnom Penh presented the results from Cambodia (Table 1). In 2008, CNM assessed the efficacy of DHAPIP (co-formulated) and atovaquone-proguanil (AP) against falciparum malaria in Veal Veng and of CQ against vivax malaria in Pailin. AS+M (co-packaged) is the current first-line drug in Cambodia. However, because of the increasing failure rates of AS+M documented in western Cambodia during the last five years, an alternative ACT (DHAPIP) and a non-ACT, atovaquone-proguanil (AP) (Malarone™), are used in the containment area Zone 1 and through mass screening / index case investigation respectively with the aim of temporarily reducing pressure on artemisinin. Table 1 shows the study outcomes in the two sites and the parasite clearance time per drug.

DHAPIP and AP had comparable efficacy levels with no significant difference in Parasite Clearance Time although AP performed better than DHAPIP pertaining to Fever Clearance Time. CQ remains fully effective in the treatment of *P. vivax* but reappearance of parasitaemia was observed in three cases at D28 and even more after 42-day follow-up. But early relapses cannot be ruled out at this point in time.

The 2009 studies started on 1 September in three sites with DHAPIP tested in Pailin, Preah Vihear and Rattanakiri. AS+M will also be tested in the last two sites if there are enough *P. falciparum* cases to be enrolled until mid-December. The main challenges faced by the CNM-NMCP TES team were the delayed release of funds and competition for skilled manpower, transportation facilities and resources with other high-budget malaria projects in the country. It was, however, clarified by Dr Christophel that the delay in the release of funds stems from the late submission of incomplete protocols e.g. lacking the national ethics committee (EC) approval or appropriate updated consent forms to WHO-WPRO TRG and leading to unnecessary correspondence with the PI. If upon TRG review, there are comments raised by the TRG, the PI needs to clearly respond to these comments quickly. The whole process can then take 2-3 months for final approval including release of funds. A suggestion was made for a two-year project plan approval to facilitate early release of funds requesting no more than an annual review and renewal of approval. This suggestion does not follow WPRO administrative financial procedures and so is not acceptable.

Table 1. *Summary of 28-day and 42-day TES results (PCR-corrected) against P. falciparum and P. vivax in Veal Veng and Pailin, Cambodia, 2008*

2008				
	Veal Veng		**Pailin**	
	DHA-PIP	**AP**	**DHA-PIP**	**CQ (Pv)**
ETF	0	0	0	
LCF	1 (1.3%)	0	1	
LPF	0	0	0	3 (5%)
ACPR (28-day)	75 (98.7%)	58 (100%)	48 (98%)	57 (95%)
PCR-adjusted 28-day ACPR	75 (98.7%)	58 (100%)	48 (98%)	

2008				
	Veal Veng		Pailin	
	DHA-PIP	AP	DHA-PIP	CQ (Pv)
Total analysis: 28-day	76	58	49	60
WTH	2	3	2	0
LFU	2	1	2	3
TOTAL	80	62	53	63
Day 1: % parasitaemia	79 (100%)	61 (98%)	51 (96%)	58 (92%)
Day 2: % parasitaemia	52 (66%)	40 (65%)	34 (64%)	13 (21%)
Day 3: % parasitaemia	6 (8%)	7 (11%)	14 (27%)	0
Day 4: % parasitaemia	0	0	2 (4%)	0
Day 0: % gametocytemia	4 (5%)	6 (10%)	9 (17%)	No data
Day 7: % gametocytemia	1 (1%)	10 (16%)	7 (13%)	No data
Status	Completed	Completed	Completed	Completed
Slide validation [internal]	Done	Done	Done	Done
Slide validation [external]	Not done	Not done	Not done	Not done
Total analysis: 42-day	74	54	47	60
ETF	0	0	0	0
LCF	1 (1.4%)	0	2 (4.3%)	0
LPF	0	0	3 (6.4%)	8 (13.3%)
ACPR (42-day)	73 (98.6%)	54 (100%)	42 (89.4%)	52 (86.7%)
PCR-adjusted 42-day ACPR	73 (98.6%)	54 (100%)	42 (89.4%)	??

China

The delegates from China could not participate due to the 60th Anniversary Ceremony of the Communist Party in China. Dr D. Bustos presented the results based on raw data sent by the co-investigator, Dr Manni Yang. In 2008, TES with CQ was carried out in Jiangsu province, central China, against *P. vivax* malaria and TES in Yingjiang postponed to 2009 due to quality concerns of AS tablets tested. In 2009, TES resumed in Yingjiang, Dehong county, Yunnan province (bordering with north-eastern Myanmar) to test AS7 against *P. falciparum* and CQ against *P. vivax* infections. The PI and staff from the Yunnan Institute of Parasitic Diseases (YIPD) suggested to perform TES with DHAPIP in Menglian, Pu'er, Yunnan province, bordering Myanmar instead of Mengla (bordering with Laos) where positive cases are almost absent. That study is under completion. Artesunate and DHAPIP tablets came from WHO and passed QA by an external laboratory. CQ and PQ tablets came from the Shanghai Chinese-Western Medicine Drug Manufacturer and had a certificate from the national company of QA batch analysis. In case of external QA analysis needed, the YIPD has kept 100 tablets of CQ. It has to be noted that the TES with CQ in Jiangsu did not follow the WHO protocol since PQ was not given at day 28 as per protocol recommendation.

Table2. *Efficacy results of DHAPIP and AS7 against falciparum malaria and CQ against vivax malaria in China, 2008-2009*

	Suining, Jiangsu Province	**Yingjiang, Dehong Municipality, Yunnan province**	**Yingjiang, Dehong Municipality, Yunnan province**	**Menglian, Pu'er city, Yunnan province**
	CQ for Pv	**CQ for Pv**	**AS7**	**DHAPIP**
ETF	0	0	0	0
LCF	0	0	1	0
LPF	0	2	1	0
ACPR	19 (100%)	45 (95.7%)	47 (96%)	20 (100%)
PCR-adjusted ACPR				
Total analysis	19	47	49	20 *

	Suining, Jiangsu Province	Yingjiang, Dehong Municipality, Yunnan province	Yingjiang, Dehong Municipality, Yunnan province	Menglian, Pu'er city, Yunnan province
	CQ for Pv	**CQ for Pv**	**AS7**	**DHAPIP**
WTH	0	6	10	0
LFU	2	2	6	0
TOTAL	21	55	65	20
Day 1: % parasitaemia	17 (90%)	42 (89%)	42 (86%)	0
Day 2: % parasitaemia	10 (53%)	4 (8%)	27 (55%)	0
Day 3: % parasitaemia	1 (0.5%)	0	15 (31%)	0
Day 3: % following external cross-check (30 Nov 2009)	-	-	14 (25%)	-
Day 0: % gametocytaemia	0	0	6 (12%)	100%
Day 7: % gametocytaemia	0	0	5 (10%)	0
Status	completed	Completed	Completed	* On-going (26/10/09)
Slide validation [internal]	Done	Done	Done	Done
Slide validation [external]	Not done	Not done	Done	Not done

The 96% ACPR (n=49) to AS7 in Dehong county with 31% (15/49) patients still positive on Day 3 (cleared on Day 4 and Day 5) is worrisome. At the time of writing of this final report, external slide validation to confirm this parasite clearance time (done in Nov 2009) showed 25% parasitaemia on Day 3. It should be interesting to compare such results with previous years' data. Preliminary results with DHA-PIP in Menglian show 100% ACPR (n=20).

100% ACPR to CQ+PQ against *P. vivax* malaria was observed in Jiangsu province keeping in mind that primaquine treatment started on Day 3 instead of Day 28 as per WHO protocol. Several patients weighing > 60

kg were under-dosed with CQ treatment. Slide validation was done in the 2008 study and is on-going for the 2009 studies. Filter paper samples have been sent to the National Institute of Parasitic Diseases (NIPD) in Shanghai for further processing.

Lao PDR

Dr Viengxay Vanisaveth presented the status of on-going studies in Laos which started in mid-June 2009. No study was performed in 2008. Since 2003, artemether-lumefantrine (Coartem™) is the first-line anti-malarial drug countrywide and quinine+doxicycline is the second-line treatment. Parenteral artesunate and quinine infusion are used to manage severe malaria. First-line drugs have been tested in five sentinel sites from 1997 to 2007 to be further reduced to three locations from 2008 due to the drastic decline in confirmed malaria cases in the country. The TES site in Savannakhet province is a research site supported by the Wellcome Trust. The three other active sentinel sites are: Luang Namtha in the north where AL and CQ are tested, Khammoune in central Laos and Attapeu in the south where AL is studied. RDT and microscopy have been used in surveys at village level showing conflicting results from the two diagnostic tools to be further investigated. Despite active case detection of positive patients in villages and screening of all fever cases in the hospitals in the three sites, the current progress status is as follows:

- no patient has been enrolled in Luang Namtha yet
- three patients enrolled in Khammoune: 2/3 ACPR, one still on follow-up
- three patients enrolled in Attapeu: 2/3 ACPR, one lost to follow-up

Lessons learned are as follows:

- The proposed TES methodology and required sample size are not appropriate in light of the drastic decline in malaria trend in Lao PDR and the limited duration of the monitoring period.
- Provincial and district staff in Khammoune and Attapeu sentinel sites show improved knowledge and experience in *in-vivo*

monitoring but more training and supervision is needed in the Luang Namtha (LNT) site.

- Human resources at sites (provincial, district staff and microscopists) are limited with competition between activities outside the TES agenda.
- Active case detection to reach the requested sample size is labour-intensive especially in LNT.

The PI from Lao PDR presented an alternative option to the classic sentinel site approach. The suggestion was to set up three regional sentinel sites (north, central and south) encompassing 2-3 provinces with the involvement of provincial and district hospitals, health centre and village volunteers in patient recruitment. The study duration might be eight months to capture two peak transmission periods and to be carried out every two years. It was suggested to explore this option, and review the budget needed in the country plan from 2010 onwards.

On the issue of discrepancy in results between blood smears (slides) and RDT, questions were raised on whether filter paper blood spots have also been taken during the hospital screening and village surveys in parallel with RDTs and slides even if not part of the protocol. Paracheck© RDTs used for screening passed QA tests made at Institute Pasteur in May 2009 and Carestart© combo RDT were procured through WHO-WPRO. Expert certified microscopists from CNM have validated the slides from TES carried out in the three sites. There is an urgent need to look at such discrepancies in greater detail and check if it is a typical 3% error rate.

Myanmar

Dr Myat Phone Kyaw from DMR Lower Myanmar presented 2007 data on malaria prevalence, morbidity rate (8.74/1000), mortality rate (2.19/100,000) and vector distribution per state and division in Myanmar. Since 2008, first-line drugs include three-day AL, DHAPIP and AS+M depending on funding sources. The country has set up six sentinel sites as follows: three along the border with Thailand, one along the border with China, one with India and one on the border with Bangladesh. Table 2 shows the ACPR results of studies (PCR-corrected) carried out in four sentinel sites in 2007 using the WHO 28-day protocol. No study was

carried out in 2008 with WHO support. Three studies are ongoing and are to be completed by December 2009.

Table 3. *Efficacy of AL and AS-AMO in four sentinel sites in Myanmar, 2007*

Drug tested / location	Mon	Kayin	Rakhine	Kachin
AL	97.6% ACPR	97.5%	97.9%	100%
AS-AMO	98.1%	97%	100%	98.5%

In a 2008 clinical trial of three-day artemisinin-piperaquine (Artequick™) at the Defense Services General Hospital in Yangon [it should be noted that patients (mainly soldiers) are admitted from various country locations], delayed parasite clearance time of >100 hours (> 4 days) was observed in 7/50 patients and >90 hours (> 3 days) in two patients. Origin of patients with delayed PCT should be further investigated.

Previous studies have shown decreasing efficacy of the following ACTs in Kawthaung, Tanintharyi division: artesunate+amodiaquine (ACPR of 92.9% and 82.2% in 2005 and 2006 respectively); to artesunate+mefloquine (ACPR of 100% and 91.1% in 2005 and 2006 respectively) and to artemether-lumefantrine (Coartem™) (ACPR of 98.3% and 91.7% respectively). Kawthaung is bordering with Ranong province in southern Thailand where results from TES with AS+M show ACPR of 87% in 2004 and 90% in 2006.[5]

Table 4 summarizes preliminary results from TES which started in June 2009 in Shwe Kyin, Bago division and Kawthaung, Thanintharyi Division. The *P. vivax* and *P. falciparum* TES in Kalay are on-going and expected to be completed by mid-November 2009. It was pointed out that the high proportion of yet positive patients at day3 with DHAPIP in Kawthaung is worrisome and needs further validation.

[5] From the presentation made by the Malaria Programme, Myanmar, on anti-malarial drug Resistance during the national workshop on Therapeutic Efficacy Studies (TES) and Malaria Technical Consultative meeting in Yangon, 10-13 March 2009.

Table 4. *Preliminary results (pending PCR) of efficacy of AL and DHAPIP in Shwe Kyin and Kawthaung, Myanmar, 2009*

	2009			
	AL		**DHAPIP**	
	Shwe Kyin	**Kawthaung**	**Shwe Kyin**	**Kawthaung**
ETF	1 (1.1%)	0	0	0
LCF	0	3 (3.9%)	0	2 (2.5%)
LPF	1 (1.1%)	1 (1.3%)	0	2 (2.5%)
ACPR (28-day)	84 (98%)	74 (95%)	100%	76 (95%)
PCR-adjusted ACPR				
Total analysis: 28-day	86	78	72	80
WTH	0	2		1
LFU	2	0	0	0
TOTAL	88	80	72	81
Day 1: % parasitaemia	72 (85.7%)	52 (66.7%)	51 (71.8%)	76 (92.8%)
Day 2: % parasitaemia	30 (35.7%)	30 (38.5%)	15 (21.1%)	54 (66.7%)
Day 3: % parasitaemia	8 (9.5%)	8 (10.3%)	3 (4.2%)	24 (29.6%)
Day 3 % parasitemia after external slide cross-check in Dec 2009	-	6 (7.5%)	-	15 (18.5%)
Day 0: % gametocytaemia	29 (34.5%)	28 (35.8%)	14 (19.7%)	11 (13.6%)
Day 7: % gametocytaemia	8 (9.5%)	1 (1.3%)	6 (8.5%)	3 (3.7%)
Status	Completed	Completed	Completed	Completed
Slide validation [internal]	Done	Done	Done	Done
Slide validation [external]	Not done	Done	Not done	Done

Challenges faced by the TES team in Myanmar are as follows: delay in starting the study in lower and central Myanmar; late onset of the monsoon in upper Myanmar, hence few malaria patients eligible for TES; and self-medication with artesunate monotherapy by many patients. On the technical side there is a need to strengthen the quality of laboratory diagnosis especially microscopy (refreshing training sessions and accreditation).

Thailand

Dr Kanungnit Congpuong, PI in BVBD-MOH, presented recent malaria data from Thailand e.g. API of 0.14/1000 and mortality rate of 0.16/100,000 in 2008. Most malaria cases are recorded in provinces along the border with Myanmar, Cambodia and Malaysia. Thailand introduced the two-day regimen of AS+M (loose tablets) in selected provinces in 1995, and adopted that regimen and dosage for the whole country until 2005, then shifted in 2008 to the three-day regimen of AS+M countrywide. With a total of nine sentinel sites, TES were carried out in six sites in 2008 and in six sites (four for *P.f.* and two for *P.v.*) in 2009. Tables 5 and 6 show results from studies performed in 2008 and preliminary results from TES in 2009.

Table 5. *Efficacy of AS+M (PCR-corrected) in six sentinel sites in Thailand, 2008*

	2008					
	Mae Hon Son	**Tak**	**Ratcha-buri**	**Ranong**	**Ubonrat-chathani**	**Yala**
	ARS-MQ	**ARS-MQ**	**ARS-MQ**	**ARS-MQ**	**ARS-MQ**	**ARS-MQ**
ETF	0	0	0	0	0	0
LCF	0	2 (3.2%)	0	1 (3%)	0	0
LPF	0	0	0	0	0	0
ACPR	42 (100%)	60 (96.8%)	50 (100%)	34 (97%)	45 (100%)	47 (100%)
PCR-adjusted ACPR	100%	96.8%	100	97%	100%	100%
Total analysis	42	62	50	35	45	47
WTH	0	0	0	0	0	0
LFU	2	3	0	12	0	7

	2008					
	Mae Hon Son	**Tak**	**Ratcha-buri**	**Ranong**	**Ubonrat-chathani**	**Yala**
	ARS-MQ	**ARS-MQ**	**ARS-MQ**	**ARS-MQ**	**ARS-MQ**	**ARS-MQ**
TOTAL	44	65	50	47	45	54
Day 1: % parasitaemia	69	25	46	49	0	22
Day 2: % parasitaemia	17	9	10	0	0	9
Day 3: % parasitaemia	5 (11%)	0	0	0	0	0
Status	Completed	Completed	Completed	Completed	Completed	Completed
Slide validation [internal]	Done	Done	Done	Done	Done	Done
Slide validation [external]	Not done	Not done	Not done	Not done	Not done	Not done

Table 6. *Preliminary results (pending study completion, slide validation and PCR) of efficacy of AS+M in four sentinel sites, Thailand, 2009.*

	2009			
	Mae Hon Son	**Tak**	**Kanchanaburi**	**Ranong**
	ARS-MQ	**ARS-MQ**	**ARS-MQ**	**ARS-MQ**
ETF	0	0	0	0
LCF	1 (6.7%)	2 (6.9%)	1 (2.6%)	2 (20%)
LPF	1 (6.7%)	3 (10.3%)	3 (7.7%)	0
ACPR	12 (86.6%)	24 (82.8%)	35 (89.7%)	8 (80%)
PCR-adjusted ACPR				
Total analysis	15	29	39	10
WTH	0	0	0	0
LFU	3	3	0	2
TOTAL	18	32	39	12
Day 1: % parasitaemia	72	56	44	92

	2009			
	Mae Hon Son	**Tak**	**Kanchanaburi**	**Ranong**
	ARS-MQ	**ARS-MQ**	**ARS-MQ**	**ARS-MQ**
Day 2: % parasitaemia	11	31	26	42
Day 3: % parasitaemia	6	19	8	0
Status	On-going	On-going	On-going	On-going
Slide validation (as of 26/10/09)	On-going	On-going	On-going	On-going

With regard to 2009 results, the required sample size in all sites has not yet been reached and patient recruitment will continue until December 2009. Hence, it is too early to draw any firm conclusions. The *vivax* studies in Chantaburi and Yala are also on-going.

Preliminary results show that ACPR in 2008 was better than 2009 at 97% - 100% in the six sites. It was acknowledged that ACPR was consistently lower in Ranong and Tak as compared to other provinces and as compared to 2006. These two provinces are on the northwestern and southwestern border with Myanmar and have always been active cross-border points with intense population movement of migrant workers and traders on both sides; hence it may be interesting to note the origin of these infections including migratory patterns. Overall, an increasing proportion of patients are still positive on day 3 since 2006. Pending sample size completion, slide validation and PCR results of the 2009 studies, preliminary results point out potential new (cross-border) critical "hot spots" to be more closely monitored for artemisinin and ACT resistance.

Issues relate to the delayed implementation of 2009 TES and a drastic decline in malaria cases in most areas especially on the Cambodia-Thailand border where AFRIMS is also supporting TES in coordination with BVBD. It was observed that there is unacceptable variation in parasite counting between microscopists in such a way that slides have to be re-examined at the BVBD.

Viet Nam

Dr Ta Ti Tinh from NIMPE, Hanoi, presented recent malaria data from Viet Nam e.g. API of 0.13/1000 and mortality rate of 0.03/100,000 in 2008. The 2009 national treatment guidelines exclude AS7 monotherapy among treatment recommendations with the emphasis on artemisinin-based combination DHAPIP as first-line drug for *P. falciparum* and CQ+PQ for *P. vivax* malaria. Nevertheless, Viet Nam needs to monitor the efficacy of AS7 (16mg/kg over 7 days) even if no longer formally in its drug policy e.g. to monitor PCT of artesunate after the beginning of its use countrywide from 1990.

In 2008, TES were carried out in two sites only: Quang Tri and Gia Lai. TES initially planned in 2008 in Dak Nong was eventually performed in 2009 in Ninh Thuan because of the quasi-absence of malaria cases in Dak Nong and the TES in Binh Phuoc was started in 2009 instead of 2008 (Table 6). TES were conducted in the same locations in 2009 with different drugs under investigation as follows: AS7 in Quang Tri, DHAPIP in Dak Nong and Binh Phuoc and CQ in Ninh Thuan and in Binh Phuoc (*P. vivax* malaria). Viet Nam has tested a locally manufactured co-formulated DHAPIP (Arterakine™) made by the Central Pharmaceutical factory No. 1, Viet Nam and artesunate tablets 50 mg from the Nam Ha Pharmaceutical factory, Viet Nam. Both locally produced anti-malarial drugs passed QA batch analysis by the national drug regulatory agency. The total dosage for one adult treatment with DHAPIP was 8 tabs (40 mg of dihydroartemisinin and 320 mg of piperaquine phosphate/tab: 4 tabs on D1 then 2 tabs on D2 and D3) over three days and with AS7 was 16mg/kg over seven days (4 mg/kg first day and 2 mg per day the next six days).

Table 7. *Efficacy results of DHAPIP and AS7 in Viet Nam, 2008*

	Binh Phuoc	**Ninh Thuan**	**Quang Tri**	**Gia Lai**
	AS7	**AS7**	**DHA-PIP (Arterakin™)**	**DHA-PIP (Arterakin™)**
ETF	0	0	0	0
LCF	4 (7.5%)	3 (7%)	1 (2%)	0
LPF	4 (7.5%)	6 (14%)	0	0
ACPR	45 (85%)	35 (79.5%)	65 (98.5%)	48 (100%)
PCR-adjusted ACPR	45 (85%)	43 (97%) *	66 (100%)	48 (100%)

	Binh Phuoc	Ninh Thuan	Quang Tri	Gia Lai
	AS7	AS7	DHA-PIP (Arterakin™)	DHA-PIP (Arterakin™)
Total analysis	53	44	66	
WTH	5	6	0	7
LFU	3	5	2	4
TOTAL	61	55	68	59
Day 1: %	46 (87%)	18 (41%)	23 (35%)	29 (60%)
Day 2: %	17 (32%)	2 (5%)	1 (2%)	2 (4%)
Day 3: %	7 (13%)	0	0	0
Day 3: % following external cross-check done 20 Nov 2009	6 (11.5%)	-	-	-
Day 0: %	No data	1	No data	No data
Day 7: %	No data	0	No data	No data
Status	Completed	Completed	Completed	Completed
Slide validation (internal)	Done	Done	Done	Done
Slide validation (external)	Done	Not done	Not done	Not done

* 8/9 LPF and LCF were reinfections

The 7-day mono-therapy with AS is still effective against *P.falciparum* malaria in Ninh Thuan but a higher failure rate (15%) is noticed in Binh Phuoc with 11.5% (after cross checking slides) of patients with parasitaemia on Day3 (as compared to 0% in other locations). DHAPIP has so far demonstrated high therapeutic efficacy, faster fever and parasite clearance than AS7, has less side effects and is well accepted by a majority of patients.

It was noted that Binh Phuoc is bordering with Snoul in Cambodia (where TES were discontinued in 2006 due to absence of positive malaria cases). It was suggested to resume TES in Snoul from 2010. Discussion centered on the possibility that artemisinin resistance is not just on the Cambodia-Thailand border and may have extended to the Thai-Myanmar, Myanmar-China and Cambodia-Viet Nam borders. To confirm such worrying results, it was suggested to perform *in vivo* TES with artemisinin monotherapy in new potential hotspots complemented by molecular fingerprinting of parasite genomes to track artemisinin resistance (gene flow).

3. Country plans

On day2 afternoon, participants were divided into working groups per country to develop their 2009 country TES POA as follows:

Table 8. *Country plans for sentinel sites, proposed budget and microscopy refresher course or retraining, 2010-2011*

	2010			2011			Requested microscopy training or refresher course
Country	**Site**	**Drugs**	**Proposed budget**	**Site**	**Drugs to test**	**Proposed budget**	
Cambodia 1	Sampouv Loun	DHA-PIP, or new ACT: AS+M if enough pts: CQ	US$ 113,800	Pailin	DHA-PIP, or new ACT: AS+M if enough pts: CQ	US$ 113,800	YES
2	Veal Veng			Ratanakiri			
3	Snoul			Preah Vihear			
China 1	Dehong, Yunnan	AS7		Dehong, Yunnan	CQ		
2	Suining, Jiangsu	CQ		Menglian, Puer, Yunnan	DHAPIP		
Lao PDR 1	Northern site			Northern site	AL	US$ 85,000	YES, including external microscopy QA
2	Central site			Central site	AL		
3	Southern site			Southern site	AL		
Myanmar 1	Myit Kyi Nar (MMR-China)	AL, DHAPIP, CQ	US$ 203,500	Kalay Tamu (MMR-India)	AL, DHA-PIP, CQ	US$ 143,500	YES, including internal/external cross-cheking
2	Punna Kyun (MMR-Bang)	AL, DHAPIP, CQ		Shwe Kyin (Central MMR)	AL, DHA-PIP, CQ		
3	Mya Wadi (MMR-Thai)	AL, DHAPIP, CQ		Kawthaung (MMR-Thai)	AL, DHA-PIP, CQ		
4	Than Phyu Zayat (MMR-Thai)	AL, DHAPIP, CQ		Mu-Se (MMR-China)	AL, DHA-PIP, CQ		
5	Kyaing Tone (MMR-Thai)	AL, DHAPIP, CQ					

	2010			2011			Requested microscopy training or refresher course
Country	**Site**	**Drugs**	**Proposed budget**	**Site**	**Drugs to test**	**Proposed budget**	
6	Kawthaung (MMR-Thai)	AS7					
Thailand 1	Tak	AS+M; CQ	US$ 63,636	Mae Hong Son	AS+M; CQ	US$ 74,242	Refresher microscopy
2	Ratchaburi	AS+M		Kanchanaburi	AS+M		
3	Yala	AS+M		Ranong	AS+M		
4	Kancahnaburi	CQ		Chanthaburi	AS+M		
5	Ranong	CQ		Ubonratchathani	AS+M		
	Chantaburi, Trat, Ubon ratchathani	AP and CQ+PQ	ARCE budget	Ratchaburi	CQ		
Viet Nam 1	Quang Tri	DHAPIP, CQ	US$ 96,206	sites to be decided after 2010 results	Decision on drugs to be tested after 2010 results	Same budget expected as in 2010	YES, every year
2	Gia Lai	DHAPIP					
3	Ninh Thuan	DHAPIP					
4	Binh Phuoc	AS7					

Cambodia

Cambodia plans for three sites in 2010 and three sites in other locations in 2011. The drugs tested will be either DHAPIP or a new ACT if therapeutic failure rate of DHAPIP is actually documented above 10% from 2008 and 2009 TES results. AS+M will be tested as well if enough patients can be enrolled (minimum 50) and CQ will be tested against *P. vivax.*

The estimated annual total budget of USD 129,800 in 2010 and 2011 does not include PCR analysis. It was mentioned that Sampouv Loun and Snoul can be re-established as sentinel sites in light of the recent increase of cases especially in Snoul province bordering with Binh Phuoc in Viet Nam where worrying results have been documented. Acknowledgement was made as well on the budget available to support TES from the Global Fund grant to the country as part of Phase II of the Rolling Continuation Channel (RCC) grant. That phase II budget is still uncertain.

It was suggested that Mekong countries in general should try to test the same drugs on both sides of the borders, specifically with Viet Nam, given the 2009 results in Binh Phuoc. The artemisinin containment project is on-going on the Thai-Cambodia border, hence Cambodia has more funding support, but human resources are not enough.

China

In China, PIs plan to perform TES in two sites in 2010 and in 2011. CQ for vivax malaria will be tested in Jiangsu province in central China and DHAPIP in Yingjiang, Dehong county in Yunnan in 2010. In 2011, CQ will be tested in Dehong and AS7 in Menglian, Pu'er City, Yunnan province. The proposed budget has still to be elaborated and submitted for review. All blood samples for PCR, slide validation and determination of CQ blood level have to be executed in laboratories in China. There is also a need to technically collaborate with experts from China to ensure that lab techniques used for TES as per WHO protocol are standardized and optimized. It includes proficiency assessment of microscopy experts especially from the province of Yunnan. In collaboration with the NIPD in Shanghai and YIPD in Simao, WHO with ACTMal has planned to make that assessment during the first quarter of 2010.

Lao PDR

Recruiting enough patients in a given period of time in current locations is a big concern in Lao PDR Therefore, researchers from Lao PDR proposed to enlarge recruitment of cases from their sentinel sites to three larger regional areas – North, Central and South. TES will be performed by using positive cases recruited in three different districts from three different provinces in the northern regional site, in three districts in two provinces from the central regional site and in three districts from three provinces in the southern regional site. AL for *Pf* and CQ for *Pv* will be tested in all three regional areas. TES performed in the northern region will include all confirmed malaria cases of whatever parasite density while TES in the two other regions will include positive cases recruited according to WHO criteria.

The proposed budget of USD 85,000 for 2011 does not include identification of lumefantrine plasma levels, G-6-PD assays, CQ blood level, PCR and training and external microscopy QA.

Although TES are planned in 2011 in the three regional sites, it was recommended to the national malaria programme to re-consider their planning in such a way that TES are conducted over 2010-11 to reduce overloaded tasks to be performed by staff in a single year. It was also suggested that Lao should not stick to strict WHO inclusion and sample size criteria in the proposed regional sites but rather monitor all positive malaria patients as indicated in the recently released WHO manual for therapeutic efficacy studies (2009). Concern was raised over the amount of work and time (with extra budget) needed to track patients. It was also suggested not to abandon the southern sentinel sites when more flexible entry criteria are used.

Myanmar

Myanmar plans to perform TES in six sentinel sites in 2010. The drug tested will be the same in all sites (AL, DHAPIP for *Pf* and CQ for *Pv*) except in Kawthaung where the seven-day artesunate regimen will be tested in 2010. In 2011, four sites are planned and the drugs to be tested in all sites will be AL, DHA PIP for *Pf* and CQ for *Pv.*

Slide results will be validated by internal and external cross-checking procedures. Technicians have been trained but where needed, refresher training courses on malaria microscopy will be organized. A retraining workshop on TES protocol implementation will be held and molecular training will be organized as well. Advocacy meetings at study sites will be supported to ensure community support.

The proposed total budget (USD 203,500 in 2010 and USD 143,500 in 2011) includes additional budget for Kyaing Tone and Kawthaung sites in 2010 including refresher training course and to conduct cross-country visits.

Partners expressed their satisfaction that molecular training was part of the plan. Concern was expressed by the number of sites (#6), whether it would be possible to recruit the number of patients and the magnitude of the budget. Matching the requested sample is possible if TES start in the middle of May at the latest. Training on TES has been done, so the capacity

of field staff to perform studies as per protocol in all selected sites is matching requirement. Pertaining to needed funds, if NMCP has to prioritize sentinel sites (from six to five), it might be possible to merge locations along the Thai-Myanmar border (e.g. Mya Wadi and Than Phyu). It is, however, necessary to keep Kawthaung as a sentinel site since previous worrying results need to be confirmed e.g. by carefully further monitoring therapeutic efficacy of artesunate over seven days. This has already been carried out in Cambodia and Thailand. Therefore, researchers from Myanmar can easily refer to the artesunate monotherapy protocol from these countries e.g. to ensure well supervised seven-day artesunate treatment. In the monotherapy protocol, PK of AS at regular intervals has to be performed. This is quite a complex procedure to be applied in the field and might need collaboration with research institutions in the region.

Exchange monitoring visits by experts / PIs e.g. between Thailand and Myanmar are encouraged as well as external monitoring visits specially in Kawthaung and Kachin state on the border with China. Partners underlined that these country and site visits are welcome but should be prepared and planned well in advance in such a way that Principal Investigators find adequate time in their schedule to perform such cross-country monitoring tasks.

Thailand

The proposed plan for Thailand in 2010 is to test both AP for *Pf* and CQ for *Pv* in three sites, AS+M for *Pf* in three sites and CQ mono- for *Pv* at three different sites. The three sites along the Thai-Cambodia border where both AP and CQ-PQ will be tested are funded separately as part of the artemisinin resistance containment project. In 2011, the proposed plan is to test both AP for *Pf* and CQ for *Pv* in one site, AS+M for *Pf* in four sites and CQ for *Pv* only in one site. The re-testing of AS+M in 2011 will be done in two sites where this treatment has been temporarily removed as first-line treatment (for two years) in order to reduce artemisinin pressure (if yet enough Pf cases). Monitoring of AS+M is expected to show declining Pf resistance to that ACT e.g. showing a proportion of patients still positive at day 3 back to 2000 rate of less than 5%. CQ will be tested in selected sites while in the ARCE sites, CQ+PQ are tested. There is a need to reconcile and consolidate *in vivo* results from TES generated by academic research institutions and BVBD.

The proposed budget with a total of USD 63,636 for 2010 and USD 74,242 for 2011 includes:

- Refresher training course in microscopy
- Cost for patient follow-up
- Data management
- PCR for the differentiation of re-infection and recrudescence
- Cost for supervision
- Cost for quality control (cross check) of microscopic examination.

Not included in the budget are the measurement of CQ blood level (PKCQ) and screening for G-6-PD deficiency. The reported prevalence of G6PD in Thailand ranges from 3% - 20 %.

Partners said that although CQ blood concentration is expensive to measure, it is mandatory to confirm the presence of CQ resistance parasite strains. The number of Pv cases showing suspected CQ resistance is expected to be low. In 2009, MORU Lab did not receive any filter papers to process PKCQ. It was also stated that lower threshold limits (than stated in the protocol) of parasitaemia density may be used to enroll more positive patients in the TES.

Viet Nam

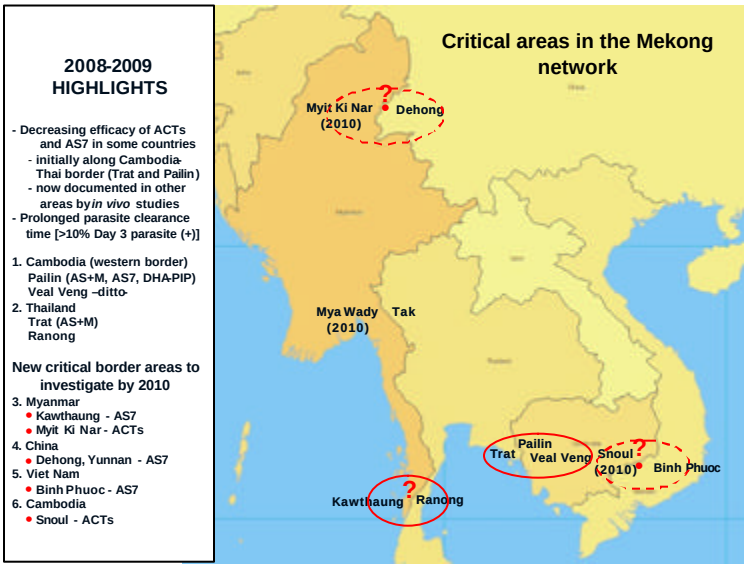
Viet Nam proposes to perform TES in four sentinel sites in 2010 and 2011. In 2010 the suggestion was to test DHAPIP in two sites, DHAPIP and CQ in one other site and seven-day artesunate again in Binh Phuoc. In 2011, the suggestion was to test DHAPIP in one site, DHAPIP and CQ in another site, AS7 in a third site and AS7 and CQ in a fourth location. It was recommended to defer the choice of drugs to be tested in 2011 according to 2010 results.

The proposed total budget (USD 96,206 per year) includes the annual training of microscopists and cross-country monitoring.

As a matter of protocol, the same drugs should be tested in the same site every two years. This is the case in three out of four sentinel sites in Viet Nam. Planning TES in Viet Nam is currently a challenge due to very low malaria transmission reached in most locations where TES are performed. Therefore, it was suggested to wait for results from 2010 studies before taking a decision on locations and drugs to be tested in 2011.

4. Conclusions and recommendations

Figure 3. ***Greater Mekong sub-region showing areas where artemisinin resistance has been confirmed and border areas where artemisinin tolerance may be emerging***



- There is an indication that artemisinin resistance might have emerged in "hot spots" other than the Cambodia-Thailand border (Pailin – Trat) in the GMS. Longer parasite clearance time (>72 hours) measured at day3 and beyond with AS7 monotherapy and ACT have been observed notably in Dehong, Province of Yunnan, China, on the Sino-Myanmar border and in Binh Phuoc province in southern Viet Nam bordering with the province of Snoul in Cambodia (Figure 3). Longer parasite clearance time and decreasing efficacy of ACTs have also been observed in Kawthaung, on the south-eastern tip of Myanmar bordering with the province of Ranong in Thailand.
- As a result, extra TES with seven-day artesunate monotherapy needs to be performed in two specific sites on the Myanmar side bordering with China (Myit Ki Nar) and Thailand (Kawthaung) to confirm (or not) the decreasing efficacy observed of ACTs during the two last years.

- Internal validation first followed by external slide validation when and where needed is perceived as an essential TES component with all PIs expressing their need to WHO to support refresher training courses in microscopy and parasite counting. This is especially important to cross-check the presence and number of parasites at Day1-3 and beyond (however, the protocol is not requesting blood slides at day 4, 5 and 6) as a critical outcome when performing TES with ACT or AS7.
- From recent preliminary (2008 and 2009) results, there is an urgent need to validate slides from TES carried out in China, Myanmar and Viet Nam especially targeting those in-patients showing delayed parasite clearance time. Accredited country "expert" microscopists from the GMS are proposed to cross-validate critical slides in these three countries.
- Preliminary *in vivo* results provide early information that artemisinin resistance may have emerged on the Thai-Myanmar, China-Myanmar and Cambodia-Viet Nam borders. Such worrying results need to be confirmed. To do so, *in vivo* TES with artemisinin monotherapy have to be carried out. In addition, molecular fingerprinting of parasite genomes has to be systematically done to track the gene flow of artemisinin resistance around the region.
- Molecular tools are equally important to confirm artemisinin therapeutic failures. The existing network of in-country molecular laboratories using standardized techniques has to be strengthened bearing in mind obstacles to exchange biological samples out of some countries (e.g. China) to regional reference laboratory centres.
- It has been agreed to have pharmacokinetic (PK) assays of chloroquine through filter paper blood samples sent / processed at the Mahidol-Oxford Research Unit (MORU) in Bangkok. No single filter paper was sent from countries to MORU in 2009 in spite of three suspected failure cases documented in Pailin in 2009. Funds have to be secured for said assays. Technical collaboration between MORU and with NIPD in Shanghai has to be initiated and maintained.
- Continuous annual monitoring is needed in some sentinel sites where critical thresholds of treatment failures are being observed. Data from these sites need to be analyzed, exchanged and validated jointly with WHO and country PIs.

- It has been suggested to perform cross-country monitoring visits involving Principal Investigators and accredited microscopists together with WHO consultants during TES implementation. This would help to ensure quality implementation of TES at field sites, enhance skills of PIs, highlight country best practices and provision of technical recommendations in a timely basis.
- The TES network is performing well as an early warning system. However, more brainstorming and cross-border planning are needed to identify practical ways and supranational Mekong tactics in terms of local response strategies and capacities in each country from a regional perspective.

Partners, donors and observers were impressed with the hard work and professionalism of country PIs and representatives from Mekong countries. Such important results should be presented to the global community soon and published once all data have been validated. From the perspectives of partners (USAID Global Health Bureau and the Bill and Melinda Gates Foundation), the work done in the GMS is a good model to be considered in Africa and other parts of the world especially in terms of close country cooperation and partnerships. Nevertheless, the value of TES and the work done must be measured against concrete actions taken as a direct result including publication of data in a collective way from the Mekong Sub-region. With additional funds from the President's Malaria Initiative (PMI) and the US strategic plan to support networks carrying out research on resistance (annex 3) partners underlined that they would be willing to give all the support they could to maintain and strengthen TES networking interventions. ACTMalaria is in a position to support training session(s) in countries; WWARN will help in the molecular networking and provide data analysis support through the website and the regional office that is soon to open in Bangkok; The Malaria Consortium will continue to support the M&E system in light of new available information; and the US-CDC perceives there are now more potential areas for collaboration. WHO stated that information presented in the workshop demonstrates that the *in vivo* MMP TES network is a good early warning monitoring system supported by all countries but preliminary data presented are very worrying. Therefore, there is a need to decide quickly on how to actively respond from a GSM perspective. With more donors forming, it might be prudent to shift to a methodology similar to that of the emerging diseases with the focus, among other things, on the assessment of the local response capacities and practical strategies to put in place and sustained.

Annex 1

Agenda

September 30th, 2009 (Day 1)

Chairperson and vice-chair: Dr Than Win and Dr Samlane Pompida

10:15	Registration of participants	
10:45	Welcome remarks	*Acting WR Myanmar*
10.50	Opening address	*Director General Department of Health*
11:30	Self-introduction, nomination of chairperson and rapporteurs Review of the draft Agenda and expected outcomes	*C. Delacollette*
11:45	Monitoring *P. falciparum* and *P. vivax* resistance to anti-malarial drugs: a global overview and progress made as part of the ARC3 project	*P. Ringwald*
12:15	Containment of Malaria Multi-Drug Resistance on the Cambodia-Thailand Border: progress made	*E. Christophel & C. Delacollette*
	Clarification	*Chairperson*
14:15	Results from TES conducted during the last 2 years in the GMS	*Chairperson*
	Cambodia Lao PDR Myanmar	
15:45	Thailand Viet Nam PR China	
	Clarification	*Chairperson*
18:00	Closure of DAY1	

October 1st, 2009 (Day 2)

Chairperson and vice-chair: Dr Khin Lin and Dr Kheng Sim

8:30	Overview of main challenges to implement TES in the GMS	*D. Bustos*
9:30	Health research involving human subjects: ethical considerations and procedures to follow	E. Christophel
9:45	Clarification and discussion	*Chairperson*
10:30	Increasing performance of TES: addressing above challenges	*Chairperson*
11:00	WWARN project and Molecular marker network: objectives and perspectives	*P. Guerin & C. Plowe*
11:30	Introduction to 2010-11 country plans	*C. Delacollette*
14:00	Working group by country	*Facilitators*
17:30	Closure of day 2	

October 2nd, 2009 (Day 3)

Chairperson and vice-chair: Dr Ye Htut and Dr Wichai Satimai

8:00	Presentation (20-minute per country) and discussion on country plans	*Chairperson*
10:30	Next steps	*C. Delacollette & P. Ringwald*
10:40	closing remarks	*Chairperson, Deputy DG, DOH*

Annex 2

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The Greater Mekong Sub-region (GMS) is known as the global epicentre of P. falciparum resistance to antimalarial drugs. The WHO Mekong Malaria Programme (MMP) in vivo Therapeutic Efficacy Study (TES) Network promotes the use of a single standardized protocol across 6 Mekong countries to monitor the efficacy of first-line antimalarial medicines recommended in the GMS. This Network has been strengthened following a WHO MMP informal consultation in January 2007 in Cambodia acknowledging the decreased sensitivity of P. falciparum to ACTs on the Cambodia-Thailand border. In Sept 2007, representatives and principal investigators (PI) from malaria control programmes of Cambodia, China, Lao PDR, Myanmar, Thailand and Viet Nam as well as partners agreed to use the updated WHO TES protocol and related case management guidelines to monitor drug resistance in 32 sentinel sites across the GMS. Patients' clinical symptoms and parasite counts were monitored during at least 28-days follow-up, adhering to strict standardized entry criteria, cross-checking slides and quality data management, and systematically using polymerase chain reaction (PCR) to differentiate re-infections from recrudescence, including genotyping and use of molecular markers for resistance. Preliminary results were presented by PIs in Mandalay, Myanmar in September 2009. Longer parasite clearance time (PCT) and decreasing efficacy rate (ACPR) of ACTs have been observed in Kawthaung on the south-eastern part of Myanmar bordering Thailand (province of Ranong) where the ACPR to AS+M has been also declining since 2006. Preliminary results also show a longer PCT (beyond day 3) to AS7 monotherapy in Dehong, Yunnan province of China bordering Myanmar, and in Binh Phuoc province in southern Viet Nam bordering Cambodia (province of Snoul). Such worrying results have been further validated. Since artemisinin resistance is not only confined on the Cambodia-Thailand border but might have extended to or spontaneously emerged de novo in the Myanmar-Thailand, China-Myanmar and Cambodia-Viet Nam borders, additional in vivo studies with 7-day artemisinin monotherapies including pharmacokinetic (Pk) assays of AS and molecular fingerprinting of parasite genomes to track artemisinin resistance (gene flow) circulating around the region are planned in 2010-2011 in the six countries. Molecular biology tools and markers are increasingly crucial to be identified / used through samples collected in the GMS. Also noted during the workshop was the increasing complexity to recruit malaria cases through a single sentinel site channel against required sample size in most of Mekong countries. New multi-district sentinel sites approaches will be discussed and piloted to address that situation.

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