Containment of Malaria Multi-Drug Resistance on the Cambodia-Thailand Border

Report of an Informal Consultation
Phnom Penh, 29-30 January 2007

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Acknowledgements

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List of acronyms and abbreviations

A3+M25	artesunate 600 mg over 3 days plus mefloquine 25 mg/kg (loose tablets)
A2+M25+PQ	artesunate 600 mg over 2 days + mefloquine 25 mg/kg + primaquine single dose (loose tablets)
A3&M25	co-blistered artesunate and mefloquine by age groups
ACT	Artemisinin-based Combination Therapy
AFRIMS	Armed Forces Research Institute of Medical Sciences
CDC	Communicable Disease Control
CNM	National Centre for Parasitology, Entomology and Malaria Control
DDF	Department of Drugs and Food (MOH Cambodia)
DHA	dihydroartemisinin
DNA	deoxyribonucleic acid
DOT	Directly Observed Treatment
FDA	Food and Drug Administration
FHI	Family Health International
GMS	Greater Mekong Sub-region
IC50	50% inhibitory concentration
IPC	Institut Pasteur Cambodia
ITM	Institute of Tropical Medicine (Belgium)
ITN	Insecticide-Treated Net
MSH	Management Sciences for Health
MSF	Médecins sans Frontières
QC	Quality Control
MDR	Multi-Drug Resistance
MOPH	Ministry of Public Health (Thailand)

NAMRU2	U.S. Naval Medical Research Unit No. 2
PCR	Polymerase Chain Reaction
PCT	Parasite Clearance Time
PFD	Partners For Development
Pfmdr1	*Plasmodium falciparum* multi-drug resistant gene
PK	Pharmacokinetics
PSI	Population Services International
RPM Plus	Rational Pharmaceutical Management Plus
SEAMEO TROPMED	Southeast Asian Ministers of Education Organization/Regional Tropical Medicine and Public Health
SEARO	WHO Regional Office for South-East Asia
TB	Tuberculosis
TDR	Special Programme for Research and Training in Tropical Diseases
TORs	Terms of Reference
USAID	United States Agency for International Development
USP/DQI	The United States Pharmacopeia/Drug Quality and Information
VC	Vector Control
WHO/HQ	World Health Organization, Headquarters
WPRO	WHO Regional Office for the Western Pacific

Background

Since the 1970s, the border area between Cambodia and Thailand has been the epicentre of emerging malaria drug resistance. This started with resistance to chloroquine, followed by resistance to sulfadoxine-pyrimethamine, then mefloquine, and currently there is an increasing failure rate of *P. falciparum* to artemisinin-based combination therapies (ACT).

In response, Cambodia and Thailand have adapted their national malaria treatment policies accordingly. Since 1995, Thailand has been using a 2-day course of artesunate in combination with mefloquine plus primaquine single dose (A2+M25+PQ) for treatment of uncomplicated falciparum malaria in selected provinces where mefloquine resistance was well documented. Cambodia adopted a 3-day course of artesunate plus mefloquine countrywide in 2000. However, the development of failures for these new regimens has occurred.

As the results of regular therapeutic efficacy monitoring conducted by the malaria control programmes of both Thailand and Cambodia show:

- In Trat, south eastern province of Thailand, 79% treatment efficacy of A2+M25+PQ was reported in 2003[1],
- In Pailin, western province of Cambodia, A3+M25 showed 86% and 90% efficacy in 2002 and 2004, respectively[2]. In Battambang province of Cambodia, a similar treatment efficacy was found (96% and 92% in 2001 and 2003, respectively),
- In Battambang province, the efficacy of another ACT regimen: artemether-lumefantrine, which has never been used in Cambodia, was found to be reduced in several studies (ranging between 71% and 87%)[3].

The high failure rates of ACTs used in the GMS constitute a regional and global emergency especially if one possible cause could be the local

emergence of falciparum resistance to artemisinin-derivatives. All current WHO-recommended treatment regimens for falciparum malaria are based on artemisinin-derivatives. If indeed artemisinin resistance is arising there is fear that it might spread to other continents, especially Africa with its very high malaria burden, as had been implied to be the case with resistance to other malaria drugs[4]. On the other hand, an unnecessary false alarm might seriously jeopardize current international initiatives to scale up ACTs and thereby gravely damage current global malaria control efforts.

This two-day informal consultation brought together the National Malaria Control Programmes of Cambodia and Thailand, other involved national authorities of the two countries, as well as partners in the implementation of malaria control programmes as well as international experts. The aim of the consultation was to review and reach a consensus on the actual malaria drug resistance status on the Cambodia-Thailand border. The consultation aimed to explore underlying reasons for the emergence of drug resistance and to set up and deploy a comprehensive and multi-sector strategy to halt the development and prevent the further spread of malaria drug resistance. Part of this strategy consisted of agreeing on a research agenda to better understand the factors contributing to the development of malaria drug resistance along the Cambodia-Thailand border.

This consultation also aimed to outline the elements of a proposal for an international initiative to intensify the containment of multi-drug resistance on the Cambodia-Thailand border which can mobilize governments and partners and generate additional funding.

The objectives of the consultation were:

(1) To review available data on the efficacy of malaria drugs and drug resistance in Cambodia and Thailand,

(2) To review current policies, current malaria control activities in the western Cambodian and eastern Thai provinces, existing initiatives/partners involved and potential causes of drug resistance,

(3) To discuss and identify necessary comprehensive and cost-effective actions to halt the development and prevent the spread of antimalarial drug resistance,

(4) To identify partners and mobilize resources.

Day 1: Is malaria MDR emerging on the Cambodia-Thailand border?

Presentations

Five presentations were made to outline the results of *in vivo* and *in vitro* studies on ACTs in Thailand and Cambodia.

(1) Dr Lon Chantap (CNM) made a presentation on *Therapeutic Efficacy of ACTs in Cambodia*. He presented the results of drug efficacy monitoring studies for A3+M25 and A3&M25 conducted between 2000 and 2006, which show that A3&M25 combination therapy is still effective in Cambodia, though there is reduced sensitivity in the western provinces. Overall, sensitivity to A3&M25 remains above 90%, with the exception of the study in Pailin in 2002 that demonstrated sensitivity of 85.7% keeping in mind that mefloquine was given under-dosed in 30% of adults due to the use of A3&M25. Also to be noted is that the sample size in the study was small leading to quite large confidence intervals around estimated results.

(2) Dr Frederic Ariey (IPC) made a presentation on *Malaria Drug Resistance in the Mekong Region*. The results he presented from *in vitro* susceptibility assays (based on IC50s for quinine, chloroquine, mefloquine and artesunate) point to the emergence of MDR strains and the disappearance of highly sensitive strains in western Cambodia since 2004. Studies using molecular markers suggest that parasites in the eastern and western parts of Cambodia have a different genetic background.

(3) Ms Saowanit Vijaykadga (MoPH) made a presentation on *Therapeutic efficacy of ACTs in Thailand*. She outlined the results of drug efficacy monitoring in nine sites across Thailand, two of which (Trat and Chanthaburi) are along the Cambodian border. Results from 2003 suggest some high failure rates to A2+M25+PQ in Trat province, though the results were not PCR-corrected. MoPH is currently conducting in Trat an A2+M25+PQ efficacy study with 42-day follow up, PCR corrected, which will be completed in November 2007. It has to be noted that therapeutic efficacy studies conducted in Thailand with ACT refer to a standard regimen of artesunate and mefloquine given over 2 days (national policy) which is not in

compliance with current WHO recommendations[5]. There was discussion on the relevance of this regimen in the reduction of documented cure rates.

(4) Dr Harald Noedl (AFRIMS) made a presentation on *Artemisinins and Amino Alcohols: In Vitro and Clinical Data from Thailand and the Region*. The results of *in vitro* and *in vivo* studies (using the Thai A2+M25 regimen) in Trat province demonstrated some clinical failures with ACTs (including one case of absence of parasite clearance until Day 7). In addition, individual isolates from patients failing 7 days of artesunate monotherapy in Cambodia after extended PCT had IC50s up to 5 times higher than the overall mean. Results of a comparative study of mefloquine and DHA IC50s between some Asian countries show a significant geographical increased trend in the number of falciparum strains with higher IC50 from Bangladesh, North-West Thailand, and South-East Thailand to Western Cambodia. Nevertheless, the clinical consequences and the prevalence/ epidemiology of increased IC50 of artesunate and DHA are so far unknown. To determine whether there is resistance, an operational definition for *P. falciparum* resistance to artemisinin derivatives is urgently needed.

(5) Dr Pascal Ringwald (WHO/HQ) made a presentation on *Antimalarial Drug Efficacy and Resistance Monitoring: Results and Limitations*. He summarized the results of therapeutic efficacy tests in Cambodia and Thailand. Among the results presented were the failure rates of combinations with artemisinin derivatives and mefloquine and artemether-lumefantrine in both countries, as well as increased PCT from clinical trials using ACTs (A3&M25 and artesunate+pyronaridine in Cambodia). Decreased *in vitro* sensitivity to artemisinin in China and artesunate in Vietnam, and also the geographical trend in Cambodia and Thailand were presented. Current knowledge on *P. falciparum* resistance or reduced sensitivity to artemisinin derivatives was also summarized. Stable artemisinin resistance in rodent malaria is now reported and amplification of the *pfmdr1* gene (or its homologue) appears to be the common genetic mechanism of resistance. It has been demonstrated from *in vitro* models that artemisinin derivatives and amino-alcohols are synergistic but also cross-resistant and that *pmdr1* increased copy

number could reduce sensitivity of *P. falciparum* to artemisinin derivatives[6].

Plenary summary

For the plenary discussion, the panel, chaired by Dr Pascal Ringwald included Dr Frederic Ariey, Dr Lon Chantap, Dr Harald Noedl, Dr Ric Price, Ms Saowanit Vijaykadga and Prof. Nicholas White.

Based on the evidence provided during the presentations, discussions were held on the following questions:

- Are ACTs failing and if so, which ones?
- Are ACTs failing because of resistance to the partner drug or is there evidence of artemisinin resistance?
- What is the definition of artemisinin resistance?
- Are additional data needed?
- If yes, what is the research agenda?

The classic definition of drug resistance as per WHO guidelines was restated as "the ability of a parasite strain to survive and/or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended but within tolerance of the subject". Distinctions were made between therapeutic failure and resistance, namely that the detection of therapeutic failure does not necessarily imply resistance to the drug. In terms of the factors driving treatment failure and possibly resistance, scientists want to know whether, using the correct dosage, there is resistance, whereas programme managers want to know whether the treatment regimen in place is appropriate and effective. The discussion therefore concentrated on understanding how much of the treatment failure outlined in the presentations was attributed to components of the drug policy – for instance, the treatment regimen – versus components of the ACTs.

Factors that contribute to treatment failure

In order to determine whether or not ACTs are failing, participants discussed the following possible contributors to treatment failure:

As **incorrect dosage** may be a key factor contributing to treatment failure, it is important to have a formulation of the correct amount of drug and to give the correct dose over the correct period of time (regimen). The appropriate dose for treatment in children varies significantly according to body weight and blister packages may not correspond to the optimal dosage by body weight, therefore it is important that the dosage be adjusted by body weight. In addition, given the weakened response of parasites to the drug regimen, a key issue to consider is whether active ingredient levels of artesunate, artemether and DHA currently administered are adequately high. One of the major issues to consider is to know if the systematic use of an artesunate regimen lower than that recommended by WHO (e.g. A2+M25 *versus* A3+M25) but maintaining the recommended total artesunate dosage at 12 mg/kg plays a role in decreasing *P. falciparum* sensitivity to ACTs.

Quality of drugs is another factor to consider in assessing treatment failure. In order to eliminate drug quality as a cause of treatment failure, the tablets need to have passed QC and must remain of good quality by the time they reach the patient. Another important issue discussed was the source of the drugs used in Thailand and Cambodia. For instance, it was mentioned that Cambodia's supply of A3&M25 has come from different producers over the past seven years due to changes in donors supplying the drugs.

PK properties of ACTs also have to be taken into account. For instance, problems with absorption of the drug can be a major contributor to treatment failure. Absorption can be increased if the drug is taken with fatty foods (in the case of lumefantrine, failure rate dropped from 30% to 17% with fatty meal[3,7] or if the dosage is split over days (in the case of mefloquine at 25 mg/kg)[8]. Therefore, questions were raised as to whether splitting the dosage would lower rates of ACT failure. Since the situation in this region is so different from the rest of the world, there was discussion on the possibility of systematically adding PK data to regular surveillance monitoring in both Thailand and Cambodia to document if the problems of treatment failure stem from inadequate absorption. It was also noted that because artemisinin derivatives are absorbed rapidly compared to other antimalarials and are difficult to measure, it is difficult to characterise the concentration profiles including peak concentrations in the blood.

Are ACTs failing?

With these contributing factors in mind, the discussion turned to answering whether ACTs are failing, and if so, which ones. It is, however, clear that the partner drugs have been failing in this region before being incorporated into ACTs. This is the case for mefloquine and, to some extent, lumefantrine belonging to the same family as mefloquine with documented *in vitro* cross resistance – partly because mefloquine has been used as monotherapy for a long time[8,9,10]**.** Similarly, in other parts of the world some ACTs are failing due to high *P. falciparum* resistance to amodiaquine and sulfadoxine-pyrimethamine[6]. So, the critical question was whether artemisinin derivatives themselves are actually failing or not against current recommended total dosage (12 mg/kg) and regimens (over 3 days) bearing in mind that treatment failures (not PCR corrected) of less than 10% after 7 days artesunate or artemether have already been described e.g. in children on the western border of Thailand between 1994 and 1996[11,12,13]. It was also noted that many cases of *resistance* are not properly documented[14,15] and *in vitro* resistance threshold has not been defined yet in a situation where there was no evidence of increased IC50 trends for artemisinin in Thailand till 1999[16].

Currently, ACTs are the only effective antimalarial drugs available, therefore identifying whether the artemisinin-derivatives component is failing is paramount in order to contain potential resistance in the region.

Following the results of *in vivo* and *in vitro* research studies provided during the presentations, there was general consensus that the Cambodia-Thailand border area is experiencing a decreased sensitivity to ACTs but bearing in mind the numerous limitations stated above e.g. different ACT regimens and doses currently in use in the two countries and the fact that it is quite impossible to determine what component or/and partner drug of the ACT is failing. Anecdotal treatment failure cases with artesunate monotherapy have been reported from western Cambodia. Results from the *in vivo/in vitro* studies from eastern Thailand and Cambodia demonstrated IC50s for artemisinin derivatives significantly higher than in western Thailand and in some of the treatment failures with artesunate monotherapy, up to 5 times the mean [H. Noedl, unpublished data]. Correlation between increased IC50s of artemisinin derivatives and increased copy numbers of *pfmdr1* as suggested in previous studies has still to be documented[8].

These results are of concern in the GMS given the associated documentation of patients with poor clinical response to ACTs. As the region appears to be experiencing a disappearance of the highly sensitive strains, it could be that less sensitive pre-existing strains are being left behind, but there has yet been no real documented evolution of falciparum strains with new levels of resistance to artemisinin derivatives. There is an urgent need to determine the definition of *P. falciparum* resistance to artemisinin derivatives and concomitantly to define early warning levels or criteria sensitive enough to pick up potential resistant strains in a timely manner.

Furthermore, individual isolates display strong variations in susceptibility to artemisinin. It was pointed out however, that resistance to chloroquine was initially discovered through anecdotal data. Questions were raised as to whether an unidentified factor was causing resistance, namely whether the parasites in eastern Thailand and western Cambodia are more resistant than elsewhere once the MDR gene amplification and expression are controlled. Also, as general principle, inter-laboratory variability may compromise comparison on data from different areas.

Of the data presented from the two countries during the consultation, the **slow PCT** following treatment with artemisinin derivatives was of greatest concern. With combination therapy, artesunate usually provides the initial rapid decrease of PCT, with 95% of patients clearing peripheral parasitaemia within 48 hours, hence if the PCT is slow despite the drug being in the blood at adequate levels, this could provide evidence that it is failing. Recent studies show that in western Cambodian provinces more than 40% of patients are still parasitaemic at 48 hours which is not the case in eastern provinces[2]. Discussion took place on how to measure adequate blood level of artemisinin in patients with increased PCT since artemisinin derivatives have a very short half life with high blood level variability which makes sampling of one day not possible (e.g. with lumefantrine and mefloquine levels on day 7). This is why emphasis was put on the need for more formal artesunate PK studies combined with *in vivo* clearance data. Splenic hypofunction and haemoglobin diseases were mentioned as alternative causes of delayed PCT: in a patient with no spleen, PCT is about three weeks[11]. Nonetheless, the cases of delayed PCT where the patient does have a spleen are a cause for concern.

There was discussion on whether **absorption, nutrition or ethnicity** could play a role in the response to treatment being so different in this region compared to elsewhere. To find out if and whether there is actually

resistance, a first step would be to exclude PK as a contributor to treatment failure. It was also mentioned that PK studies should be conducted to determine whether increasing the dosage of artemisinin derivative could overcome decreased sensitivity or whether the concentration has already reached the threshold after which better efficacy cannot be obtained.

On the issue of optimizing drug regimens, there was discussion on extending the current artesunate treatment regimen in Thailand from two to three days. Since Cambodia currently has a three-day regimen, questions were raised on whether the same treatment regimen should be applied on both sides of the border. In theoretical terms, three-day regimens obtain greater benefit from artesunate because artesunate reduces 10,000 parasites per cycle and two-day regimens would only allow for one cycle[17,18]. Ultimately, it was agreed that Thailand would review the evidence base on efficacy and compliance for two- versus three-day artesunate regimens with 25 mg of mefloquine before considering whether or not to change its current two-day practice. To this end, AFRIMS is undertaking a study to compare two- versus three-day regimens in Thailand.

If drug concentrations are adequate and PK is not a problem, this would point to the presence of parasite resistance to the drug used. Participants discussed the three possibilities for why parasites would persist in the body (1) artemisinin could get broken down in erythrocytes so that its concentration is reduced once it reaches the parasite, (2) some parasites lie dormant in the body, then become active and cause recrudescence, but are not resistant (D. Kyle, personal data), and (3) the parasites are intrinsically resistant. Of these three scenarios the latter case is of greatest concern.

Recommendations of day 1

Improving the methodology for studying/assessing treatment failure and resistance

(1) Based on the discussion on *treatment failure* and *resistance*, participants suggested that the definition for artemisinin derivatives resistance should include the following parameters: (i) *parasitological failure with increased PCT (to be determined) after 7 days artemisinin derivative monotherapy,* (ii) *in spite of adequate drug levels (to be determined) in the blood,* and

(iii) *with highly elevated IC50 (to be determined) or/and modification in the genotype (to be determined).*

(2) In discussing the research agenda, it was agreed that to better assess whether there is resistance to ACTs in the region, the following additional data are needed as part of the field methodology and data analysis:

(a) PK data,

(b) information on the parasite-sensitive strains reduction ratio in a population and in individuals,

(c) information on parasite genetic population structure (linked to b),

(d) detailed information by examining in greater detail the pfmdr1 copy numbers and expression levels to see whether there is a change in the risk associated with this molecular marker (e.g. to document another mutation emerged accounting for the discrepancy in failure rates), and

(e) gametocyte carriage rates in the study population to look for increased trend.

(3) Participants also identified the factors listed below as essential requirements for the methodology of assessing treatment failure:

(a) QC of study drugs must be assured and the source of these drugs must be consistent. WHO can provide clinical trials with drugs free of charge, upon request,

(b) Dosage and regimen: Ensuring the correct dosage and regimen for artemisinin derivatives and mefloquine is an important aspect of efficacy monitoring. Studies on alternative treatment strategies (such as increasing or splitting the dose over several days) and efficacy studies of new antimalarial drugs need to be conducted to identify measures for improving the efficacy of ACTs,

(c) PK: Basic PK data is needed as a test of adequate drug concentration levels in the patient's blood which is still difficult with artesunate which may require serial measures,

(d) Sampling: The inclusion criteria may need to be revised to ensure an adequate sample size. Since this is not always easy to obtain given that surveillance is limited by the

number of patients at the sites, the possibility of conducting active surveillance was raised. To the extent possible, children must be included in the sample to reduce selection bias (since 2005, Cambodia has started including children aged under 5 years),

(e) Analysis: the use of survival analysis versus per protocol analysis is an important issue in settings where re-infection and relapses with P. vivax are common,

(f) Sharing results: It was recommended that isolates and DNA materials be shared among labs in the region to reproduce results. If possible, methodologies for clinical testing should be standardized so that results can be compared, first between the two countries and later on between Mekong countries. WHO is preparing a document on in vitro standardization with a training workshop planned in Phnom Penh in March 2007.

Network of reference laboratories

Participants agreed to establish a **network of reference laboratories**, initially across Thailand and Cambodia, and eventually covering the Mekong region. Within this network, reference centres and labs could include, among others, Mahidol University, AFRIMS and Institut Pasteur. The network would facilitate the development and use of agreed upon **standard operating procedures** in laboratories, such as for molecular or satellite markers and PK analysis. Through the network, parasites, **especially individual isolates that are potentially resistant,** would be shared between the reference labs e.g. to cross check and reach a consensus on lab results, to investigate further on parasite genotypes through DNA sequencing and to consolidate resistance intelligence.

Cambodia-Thailand Malaria MDR Task Force

Through funds available from scientific partners and interested donors, a **Cambodia-Thailand Malaria MDR Task Force** is to be set up to ensure that the research network develops its agenda against agreed upon TORs and targets. Identified immediate products of the task force/network to be considered in 2007 are as follows (taking into account the above recommendations on study methodology):

(1) conducting therapeutic efficacy studies with 7-day regimen of artesunate in Pailin,

(2) comparing efficacy of this regimen with A3&M25.

The task force is to be established and will start working as soon as possible under the coordination of the Mekong Malaria Programme.

Day 2: Response to malaria MDR

Presentations

The presentations detailed the history of drug resistance in the region and provided an overview of current malaria control policies and activities on both sides of the Cambodia-Thailand border.

(1) Dr Chansuda Wongsrichanalai (NAMRU2, Cambodia) made a presentation on *History of emergence of drug resistance at the Cambodia-Thaland border*. She provided a historical overview of the emergence and spread of parasite resistance to chloroquine, sulfadoxine-pyrimethamine, and mefloquine, all of which originated on the Cambodia-Thailand border. Elements of the subsequent changes in drug policy in Thailand were discussed. Drawing lessons from the past, there have been improvements in detecting and monitoring resistance, and faster implementation of drug policy changes in response to evidence of resistance. A compilation of recent observations on the decline of the efficacy of artesunate-mefloquine combination (A2+M25 regimen) on the Cambodia-Thailand border was also presented. Concerns over delay in early parasite clearance were raised.

(2) Dr Tol Bunkea (CNM) made a presentation on *Malaria Situation in the Cambodia-Thailand Border*. He detailed temporal trends in the incidence of malaria cases and the malaria mortality rate, and noted the increasing number of *P. vivax* along the Cambodia-Thailand border since 2002.

(3) Dr Kheng Sim (CNM) made a presentation on *Drug policy and potential factors influencing MDR and malaria control measures in Cambodian provinces bordering Thailand*. She outlined the current malaria treatment policy and strategies in Cambodia and

drew attention to the high reliance of the population on private providers for treatment, many of whom do not conduct parasite-based diagnose.

(4) Dr Wichai Satimai (MoPH) made a presentation on Epidemiology of Malaria, Drug Policy and Malaria Control Measures in Thai Provinces Bordering Cambodia and Potential Factors Influencing MDR from Thai Perspectives. He provided an overview of the national malaria drug policy and noted key elements of the malaria control programme in Thailand. Malaria control activities that were presented included: routine monitoring of drug resistance, the provision of rapid diagnostic tests in remote areas, the distribution of ITNs and community participation in malaria control.

(5) Mr Dumrong Thitikornkovit (FDA, Thailand) made a presentation on *Post Marketing Surveillance Survey of the Quality of Antimalarial Drugs on the Market*. The survey was conducted in drugstores and grocery stores to investigate the issue of counterfeits in the Thai provinces bordering Cambodia, Myanmar and Laos. Seventy-two percent of drug samples were sent for testing, of which 12% were found to be substandard. Unregistered artesunate products were found on the Thai/Myanmar border.

(6) Dr Lon Chantap (CNM) made a presentation on *Strategy to Contain Drug Resistance: Overview of the Cambodian GFATM Round 6 Proposal*. The presentation focused on the approved proposal's first objective, namely, to halt the development and prevent the spread of antimalarial drug resistance in Cambodia. Strategies to reach this objective consist of improving the quality of antimalarial drugs and combating counterfeit drugs, improving the rational use of antimalarial drugs, and intensifying malaria control activities in the western border provinces.

Plenary summary

The panel for the plenary discussion was chaired by Prof. Nicholas White and included Ms Olya Duzey, Dr Sauwakon Ratanawijitrasin, Dr Pascal Ringwald, Dr Wichai Satimai, Dr Duong Socheat and Ms Catherine Wangui Wachira.

There was discussion to understand why drug resistance developed in the Cambodia-Thailand border areas, particularly in the Cambodian province of Pailin. It is possible that the parasites in this region have **an intrinsic genetic background** that renders them more susceptible to drug resistance. Moreover, high drug pressure resulting from the chloroquinized salt project carried out in Pailin during the late 1950s contributed towards the resistance basis of parasites in this region. During the ruby rush of 1977-1992, **the high degree of movement among gem miners** in and out of Pailin and Borai played a role in the spread of resistance in the past across provinces and countries[19].

The discussion also addressed the current challenges malaria control programmes face in preventing drug resistance in the region. **Drug quality** studies have pointed out the availability of counterfeit and substandard drugs as a problem in the region, particularly in Cambodia where **the private sector** is the first point of contact for most people (>70%) seeking malaria treatment. It was noted though that since Cambodia has started providing ACTs in blister packs rather than as loose tablets, the prevalence of fake drugs has declined. **In Thailand, over-the-counter sale of antimalarial drugs is banned** and all private hospitals need permission from the MOPH to sell antimalarial drugs. There is also evidence in both countries of **drugstores supplying antimalarials that are no longer recommended by the national programme**, such as chloroquine and sulfadoxine-pyrimethamine.

Irrational drug use was cited as a significant problem in the region. As a result of irrational drug use, sub-therapeutic concentration of the drug kills most but not all parasites, thereby selecting for resistant strains. Therefore, it was stressed that **providing and completing the correct treatment regimen** is critical for preventing the initial emergence of resistance. **Over prescription** including irrational cheap products was identified as a problem, particularly in the unregulated private sector, where sales are important from a business perspective. On the end-users' side, it was mentioned that in the parts of Cambodia that are former areas of conflict, the practice of self-treatment for malaria has persisted. Failure to complete the A3&M25 course was also identified as a common problem. Even if co-blistered combinations seem to increase adherence to the recommended full treatment[20], **there was evidence of patients only taking the artemisinin tablets** out of the blister to avoid the adverse side effects of mefloquine [MOH/CNM, unpublished data].

Representatives from the CNM pointed to challenges related to **access and availability of drugs**. Access to treatment is particularly a problem among the **migrant population** on both sides of the border, mainly due to lack of awareness of where to receive treatment.

The CNM also faces difficulties in providing an adequate and continuous supply of ACTs, particularly in the remote, forested border areas. Linked to this issue is the high cost of ACTs in Cambodia, which has dropped to 65 cents from $5 in 2000, but remains prohibitive for many. Both the lack of supply and the high cost of ACTs have led to people resorting to **monotherapies** as an alternative to ACTs.

The importance of **vector control** (VC) measures was also discussed, not only in terms of prevention but also recognizing the importance of VC in decreasing the size of the parasite population and perhaps circulation of resistant parasites in the population. In Cambodia, ITNs remain effective but the CNM faces challenges in re-impregnating and distributing nets to populations living in remote parts of the country /border areas. This problem has been compounded by delays in procurement, particularly for long-lasting insecticidal nets. It was mentioned that in the forest environment, mosquitoes bite between 6pm and 10pm which needs to be addressed by alternative personal protection materials to ITNs. Therefore, beside classic ITNs for beds, nets for hammocks are highly recommended. However, behavioural studies of forest workers are needed to adapt this personal protection and to improve the coverage. The emergence of counterfeit insecticide was also noted.

Recommendations of day 2

(1) Even if resistance to artemisinin derivatives appears to be only anecdotal and not sufficiently documented on the Cambodia-Thailand border, it is necessary to plan for the eventual development of resistance strains, particularly in light of the high level of drug resistance that this region has experienced in the past. Among the most contributing factors identified to malaria MDR were the deployment of sub-therapeutic ACT regimens and inadequate adherence. In addition, either fake drugs, poor absorption, wrong dosages or wrong regimens contribute to sub blood level concentrations. A major goal then in combating new drug resistant strains is to ensure that highly efficacy regimens are used across Mekong countries to eliminate them.

In view of the existing challenges facing malaria control interventions in the region, participants recommended the following key control measures or interventions to prevent the emergence and spread of resistance on the Cambodia-Thailand border and further in the GMS:

Drug quality: Emphasis must be placed on strengthening activities to monitor the quality of antimalarials, in order to tackle counterfeit and substandard drugs. To this end, the USP/DQI is currently designing the methodology for a randomized study on drug quality in three Cambodian provinces and two Thai provinces on the border. Another recommendation was to include adverse drug reaction studies in drug quality monitoring activities.

Treatment protocols: Treatment policies need to be strengthened in the public and private sectors so that ACTs are provided based on a quality diagnosis, namely through the use of microscopy and rapid diagnostic tests. To prevent susceptibility to resistance, the optimal drug dosage must be provided from the start. Measure must also be taken to ban monotherapies in particular ban of arteminisinin monotherapy for the treatment of uncomplicated malaria.

Use and adherence: Co-blistered packs and far better co-formulation are recommended so that the right dosage is easier to follow or cannot be split. Regarding adherence, more studies are needed to understand why patients do not comply with treatment. In addition, for Thailand and Cambodia should consider adopting common treatment regimens in the border areas. Another recommendation to improve adherence was to consider whether there is a role for Directly-Observed Treatment (DOT) for malaria, as has been done for TB treatment.

Availability: Improvements in the supply, management system and better forecasting techniques need to be developed to overcome shortages of drugs and ITNs. It was suggested that task forces be established to follow up on the stock of antimalarials in the public and private sectors, as has been done in Cambodia with other drugs.

Access: Recommendations were made to support mobile teams and construction of roads to access migrants and other hard-to-reach populations. Support was also requested for health education and messages to increase awareness of prevention and treatment options among migrants on both sides of the border.

Cross-border strategies: Participants from the national malaria programmes of Thailand and Cambodia discussed harmonizing their malaria control strategies to share information on drug resistance and follow-up on patients who regularly cross the border. It was suggested that districts on the Cambodia-Thailand border jointly conduct studies on drug resistance.

Funding mechanisms: Thailand and Cambodia can seek funding for the above activities by submitting proposals to the Global Fund to Fight AIDS, TB and Malaria, either jointly or separately. Through its South-East Asia and Western Pacific Regional Offices, WHO can provide both countries with technical assistance on the proposals and can help find transitory funding.

(2) Public health authorities from Cambodia and Thailand are committed to strengthening collaboration in malaria control at the national and district levels. Participants' recommendations to put this commitment into practice were as follows:

(a) Through regional mechanisms facilitated by the Mekong Malaria Programme office, a working group be established to share information on drug resistance and harmonize malaria control activities on both sides of the border,

(b) The Mekong Malaria Programme will also help facilitate the development of a comprehensive proposal to address malaria multi-drug resistance in the region based on the above technical recommendations.

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Annex 1

Agenda

Day 1: 29 January 2007

08:00–08:30	Registration	
08:30–08:35	Welcome speech	*Dr Kheng Sim*
08:35–08:40	Remark speech	*Dr Wichai Satimai*
08:40–08:45	Remark speech by WHO in Cambodia	*Dr Michael O'Leary*
08:45–08:50	Introduction to the consultation	*Dr Pascal Ringwald*
08:50–09:00	Opening speech	*Dr Doung Socheat*
09:00–09:10	Introduction of participants, nomination of chairperson, rapporteurs and facilitators	*Dr Charles Delacollette*
09:10–09:30	Therapeutic efficacy of ACTs in Cambodia	*Dr Lon Chanthap*
09:30–09:50	In vitro tests and molecular markers focusing on artemisinins and amino alcohols in Cambodia	*Dr Frederic Ariey*
09:50–10:15	Discussions	Chairperson: *Dr Doung Socheat*
10:45–11:05	Therapeutic efficacy of ACTs in Thailand	*Mrs Saowanit Vijajkadga*
11:05–11:25	In vitro tests and molecular markers focusing on artemisinin and amino alcohols in Thailand	*Dr Harald Noedl*
11:25–11:50	Situation of drug resistance in the region, summary of data from the Cambodia-Thailand border and limitations of available data	*Dr Pascal Ringwald*
11:50–12:30	Discussions	Chairperson: *Dr Doung Socheat*
14:00–17:00	Plenary discussion on drug resistance data from the Cambodia–Thailand border	Facilitator: *Dr Pascal Ringwald*

	• Are ACTs failing? • Which ones? • Are ACTs failing because of resistance to the partner drug or is there evidence of artemisinin resistance? • What is the definition of artemisinin resistance? • Are additional data needed? • If yes, what is the research agenda?	
17:30–18:00	Presentation of key round table outcomes	Rapporteur: *Dr Harald Noedl*

Day2: 30 January 2007

08:00–08:30	History of emergence of drug resistance at the Cambodia–Thailand border	*Dr Chansuda Wongsrichanalai*
	Discussions	
	Malaria situation on the Cambodia–Thailand border	*Dr Tol Bunkea*
08:30–09:00	Drug policy and potential factors influencing MDR and malaria control measures in Cambodian provinces bordering Thailand	*Dr Kheng Sim*
	Discussions	
09:30–10:00	Epidemiology of malaria, drug policy and malaria control measures in Thai provinces bordering Cambodia and potential factors influencing MDR from Thai perspective	*Dr Wichai Satimai*
	Discussions	
10:30–11:00	Epidemiology of malaria, drug policy and malaria control measures in Thai provinces bordering Cambodia and potential factors influencing MDR from Thai perspective	*Dr Wichai Satimai*
11:00–11:10	Post-marketing surveillance survey of the quality of antimalarial drugs on the market	*Mr Dumrong Thitikornkovit*
	Discussions	
11:10–11:30	Strategy to contain drug resistance: Overview of the Cambodian GF Round 6 proposal	*Dr Lon Chanthap*

11:30–12:30	Plenary discussion: Why did drug resistance develop in this region?	Facilitators: *Dr Duong Socheat,* *Dr Wichai Satimai*
14:00–17:30	What should be included as the main interventions in a proposal addressing malaria MDR? • Case management • Harmonization of policy and/or new drug policy • Drug quality • Private sector • Vector control • Migrants • Partners and funds needed	Facilitator: *Prof. Nicholas White*
15:50–16:15	Presentation of main outcomes	Rapporteur: *Dr Ric Price*
16:15–17:00	Concluding remarks	*Dr Wichai Satimai* *Dr Charles Delacollette* *H.E. Dr Chou Yin Sim*

Annex 2

List of participants

Cambodia

CDC

Dr Bun Sreng
Director
Communicable Disease Control Department
Ministry of Health, Cambodia

Dr Chea Moneth
Deputy Director,
Country Cambodia Contact Person for
Cambodia-Thailand-Viet Nam-Lao Border
Health Cooperation
CDC Department
MoH, Cambodia

CNM

H.E. Dr Duong Socheat
Director of National Centre for Parasitology
Entomology and Malaria Control Programme
#372 Monivong Blvd.
P.O. Box 1062, Phnom Penh
Tel: +855 23 996 202
Fax: +855 23 996 202
E-mail: socheatd@cnm.gov.kh

Dr Kheng Sim, MD, MPH
Deputy director of National Malaria
Programme
#372 Monivong Blvd., P.O. Box 1062, Phnom
Penh
Tel: +855 23 996 202
Fax: +855 23 996 202
E-mail: khengsim@cnm.gov.kh

Dr Lon Chanthap
Deputy Director
National Centre for Parasitology
Entomology and Malaria Control Programme
#372 Monivong Blvd.
P.O. Box 1062, Phnom Penh
Tel: +855 23 996 202
Fax: +855 23 996 202
Email: chanthapl@cnm.gov.kh

Dr Chea Ngoun
Deputy Director of CNM
#372 Monivong Blvd.
P.O. Box 1062, Phnom Penh
Tel: +855 23 996 202
Fax: +855 23 996 202
E-mail: ngounc@cnm.gov.kh

Dr Soun Seila
#372 Monivong Blvd.
P.O. Box 1062, Phnom Penh
Tel: +855 23 996 202
Fax: +855 23 996 202

Dr Tol Bun Kea
Chief of epidemiology unit,CNM
#372 Monivong Blvd.
P.O. Box 1062, Phnom Penh
Tel: +855 23 996 202
Fax: +855 23 996 202

Dr Chiv Lim
Chief of Parasitology, CNM
#372 Monivong Blvd.
P.O. Box 1062, Phnom Penh
Tel: +855 23 996 202
Fax: +855 23 996 202

Dr Sok Poeu
#372 Monivong Blvd.
P.O. Box 1062, Phnom Penh
Tel: +855 23 996 202
Fax: +855 23 996 202

Mr Ouk Rada
#372 Monivong Blvd.
P.O. Box 1062, Phnom Penh
Tel: +855 23 996 202
Fax: +855 23 996 202
E-mail: ouk_rada@cnm.gov.kh

Dr Siv Sovanaroth
#372 Monivong Blvd.
P.O. Box 1062, Phnom Penh
Tel: +855 23 996 202
Fax: +855 23 996 202

Dr Tho Sochantha
Chief of Technical Office
#372 Monivong Blvd.
P.O. Box 1062, Phnom Penh
Tel: +855 23 996 202
Fax: +855 23 996 202

Dr Top Sophornarant
#372 Monivong Blvd.
P.O. Box 1062, Phnom Penh
Tel: +855 23 996 202
Fax: +855 23 996 202
E-mail: sophornarant@cnm.gov.kh

Ms Ngau Vanthon
#372 Monivong Blvd.
P.O. Box 1062, Phnom Penh
Tel: +855 23 996 202
Fax: +855 23 996 202
E-mail: vanthonn@cnm.gov.kh

Ms Phork Pheak Roth (Secretary)
#372 Monivong Blvd.
P.O. Box 1062, Phnom Penh
Tel: +855 23 996 202
Fax: +855 23 996 202

Mr Neng Khouy (Secretary)
#372 Monivong Blvd.
P.O. Box 1062, Phnom Penh
Tel: +855 23 996 202
Fax: +855 23 996 202

Ms Chan Davy (Secretary)
#372 Monivong Blvd.
P.O. Box 1062, Phnom Penh
Tel: +855 23 996 202
Fax: +855 23 996 202

DDF

Dr Amada Torr
Pharmacist Management Adviser
Department of Drug and Food
Ministry of Health
#8, 109 St (Ung Pokun) Phonm Penh
Tel: +0 92 234 811

Dr Chroeng Sokhan
Department of Drug and Food
Ministry of Health
#8, 109 St (Ung Pokun) Phonm Penh
Tel: +855 12 862 010
Fax: +855 23 880 696
E-mail: sokhan_c@online.com.kh

Provincial health departments

Oddormeanchey

Khourn Pong

Plong Thom

Preah Vihear

So Lain

Um Line

Koh Kong

Chhun Huor

Keth Vuthy

Pursat

Ung Sophoan

Heng Somony

Battambang

Thong Chharann

Ouk Vithiea

Pailin

Soun Chen

Yok Sovann

Banteaymeanchey

Chhum Vannarith

Keo Sopheaktra

MSF

Dr Kheang Soy Ty
MSF-B Medical Coordinator
E-mail: MSFB-Phnom-Penh-Med@brussels.msf.org

NAMRU2

Dr Chansuda Wongsrichanalai
Senior Investigator
Parasitic Diseases Programme
Naval Medical Research Unit
NIPH Office
Tel: +855 12 798 532
E-mail: dr.chansuda@gmail.com

IPC

Dr Frederic Ariey
Institut Pasteur in Cambodia
5, Monivong Blvd.
P.O. Box 983 Phnom Penh
E-mail: fariey@pasteur-kh.org

Dr Steenkeste Nicolas
IPC, Cambodia

PSI

Mr Andrew Boner and Ms Diane Freeman
PSI/Cambodia
Tel: +855 12 798-341
Fax: +855 23 218 735
E-mail: aboner@psi.org.kh
dfreeman@psi.org.kh

USAID/Cambodia

Mr Jonathan Ross
Deputy Director
Office of Public Health
U.S. Agency for International Development
#1, Street 96, Sangkat Wat Phnom
Khan Daun Penh, Phnom Penh
Tel: +855 23 728 300 #8390
Fax: +855 23 430 263
E-mail: jross@usaid.org

Dr Chak Chantha
U.S. Agency for International Development
#1, Street 96, Sangkat Wat Phnom
Khan Daun Penh, Phnom Penh
Tel: +855 23 728 300
Fax: +855 23 430 263
E-mail: cchak@usaid.gov

WHO/Cambodia

Dr Chang Moh Seng,
Scientist DHF
WHO, Cambodia
E-mail: Changm@cam.wpro.who.int

Prof. Mey Bun Denis,
WHO, Cambodia
E-mail: denism@cam.wpro.who.int

Dr Yeang Chheng,
WHO, Cambodia
Tel: 012 322 863

Participants outside Cambodia

ACTMalaria Foundation, Inc.

Ms Cecilia Hugo
Executive Coordinator
ACTMalaria Foundation, Inc.
11th Floor, Ramon Magsaysay Centre Bldg.
1680 Roxas Boulevard, Malate Manila
Philippines
Tel: (632)536-56-27; Fax/Tel: (632) 536-09-71
E-mail: cecil_hugo@actmalaria.org

RPM Plus

Ms Olya Maria Duzey
Program Manager for Asia and the Near East
Center for Pharmaceutical Management
Management Sciences for Health
4301 N. Fairfax, Suite 400
Arlington, VA 22203 USA
Tel: 703-248-1605 (direct)
Fax: 703-524-7898
E-mail: oduzey@msh.org

Ms Valerie Chambard
RPM Plus

ITM

Prof. Marc Coosemans
Unit of Vector Control
Dept of Parasitology
Prince Leopold Institute of Tropical Medicine
Nationalestraat 155
2000 Antwerp
Belgium
Tel: 32 3 247.63.12
Fax: 32 3 247 63 59
E-mail: mcoosemans@itg.be

AFRIMS

Dr Harald Noedl
Dept. of Immunology and Medicine
Armed Forces Research Institute of
Medical Sciences
315/6 Rajvithi Road
Bangkok 10400, Thailand
Tel: +66 2 644 5775
Fax : +66 2 644 4784
E-mail: harald.noedl@meduniwien.ac.at

Dr Mark Fukuda
Dept. of Immunology and Medicine
Armed Forces Research Institute of
Medical Sciences (AFRIMS)
315/6 Rajvithi Road
Bangkok 10400, Thailand
Tel: 66-2-644-5775
Fax: 66-2-644-4784
E-mail: mark.fukuda@afrims.org

Dr Delia Bethel
Armed Forces Research Institute of
Medical Sciences (AFRIMS)
315/6 Rajvithi Road
Bangkok 10400, Thailand
Tel: 66-2-644-5775
Fax: 66-2-644-4784

Krisada Jongsakul
Armed Forces Research Institute of
Medical Sciences (AFRIMS)
315/6 Rajvithi Roa
Bangkok 10400, Thailand
Tel: 66-2-644-5775
Fax: 66-2-644-4784

Dr Kurt Schaecher
Armed Forces Research Institute of
Medical Sciences (AFRIMS)
315/6 Rajvithi Road
Bangkok 10400, Thailand
Tel: 66-2-644-5775
Fax: 66-2-644-4784

Menzies School of Health Research

Dr Ric Price
Senior Research Fellow
Menzies School of Health Research, PO Box
41096, Casuarina, Darwin, NT 0811, Australia
Tel: (61) 8 8922 8197
Fax: (61) 8 8922 8429.
E-mail: ricprice@doctors.org.uk

Mahidol University

Prof. Nicholas J. White
Wellcome Trust Southeast Asian
Tropical Medicine Research Units
Faculty of Tropical Medicine
Mahidol University
420/6 Rajvithi Road, Bangkok 10400, Thailand
Tel: +66 2 354 9172
Fax: +66 2 354 9169
E-mail: nickw@tropmedres.ac

MoPH Thailand

Dr Wichai Satimai
Director, VBDC
Department of Disease Control
Ministry of Public Health
Nonthaburi 11000, Thailand
Tel: +66 2 590 3145
Fax: +66 2 591 842
E-mail: wichaisatimai@yahoo.co.th

Ms Saowanit Vijaykadga
Technical Officer, VBDC
Department of Disease Control
Ministry of Public Health
Nonthaburi 11000, Thailand
Tel: +66 2 590 3145
Fax: +66 2 591 842
E-mail: Saowanit@health.moph.go.th

Ms Pamornrat Asavasena
Public Health Officer/Chief of International
Collaboration Section
Planning Division
Department of Disease Control
Ministry of Public Health
Nonthaburi 11000, Thailand
Tel: +66 2 590 3250
Fax: +66 2 965 9588
E-mail: pmrat@health.moph.go.th

Dr Suwat Tor Warapanit
Preventive Medical Expert
Trad Provincial Chief Medical Office
6 Chaiyamongkol Rd., Trad 23000, Thailand
Tel: +66 81-377 7495
Fax: +66 39 530347
E-mail: suwatdidsay@yahoo.com

Dr Rawee Siriprasert
MoPH, Thailand

Dr Chumpol Suwan
Acting Provincial Chief, Medical Officer
Chanthaburi Provincial Chief Medical Office
Talat Sub-district, Muang District
Chanthaburi, Thailand
Tel: +66 39 311 166 #211, +66 81-940 8672
Fax: +66 39-311 553
E-mail: chumpol2000@chaiyo.com

Mr Damrong Thitikkornkovit
Post-Marketing Inspection Division
Food and Drug Administration
Ministry of Public Health

SEAMEO-TROPMED

Prof. Polrat Wilairatana
TROPMED, Mahidol University
420/6 Rajavithee Rd., Bangkok 10400
Tel: +66 2 354 9100 #t1454
Fax: +66 2 354 9168
E-mail: tmpwl@mahidol.ac.th

Chulalongkorn University

Dr Sauwakon Ratanawijitrasin
Faculty of Pharmaceutical Science
Chulalongkorn University
E-mail: sauwakon.r@gmail.com

KENAN

Dr James Hopkins
Program Manager, Public Health Programme
Kenan Institute Asia
Siripanich Building 4th floor
191 Huay Kaew Road, Muang District
Chiang Mai 50200
Tel: +66 053 213039
Fax: +66 053 213039
E-mail: jimh@kiasia.org

USP/DQI

Ms Ans Timmermans
Project Coordinator for SE Asia
The United States Pharmacopeia Drug Quality and Information
Program International Affairs Department
The United States Pharmacopeia
12601 Twinbrook Parkway Rockville
MD 20852-1790

Ms Catherine Wangui Wachira
Director
The United States Pharmacopeia Drug Quality and Information
Program International Affairs Department
The United States Pharmacopeia
12601 Twinbrook Parkway Rockville
MD 20852-1790

Dr Souly Phanouvong
Manager, Drug Quality Assurance and Policy Development
The United States Pharmacopeia Drug Quality and Information
Program International Affairs Department
The United States Pharmacopeia
12601 Twinbrook Parkway Rockville
MD 20852-1790
Tel: +1 301- 816-8582
Fax: +1 301- 816-8374
E-mail: sxp@usp.org

PFD

Dr Philippe Guyant
Malaria Programme Manager
26, St 334, Boeung Keng Kang I
Khan Chamcamnorn PO Box 551
Phnom Penh, Cambodia
E-mail: ph.guyant.pfd@online.com.kh

FHI

Dr George Watt
Associate Director, Technical Division
FHI - Asia Pacific Regional Office
Bangkok, Thailand

WHO Secretariat

Dr Rashid Abdur
Medical Officer
Malaria, Other Vector-borne and Parasitic diseases,
WHO/Cambodia
E-mail: rashid@cam.wpro.who.int

Dr Eva Maria Christophel
WHO/Regional Office for the Western Pacific
UN Avenue, Manila 1000, P.O. Box 2932
Philippines
Tel: +63 2 528 9756
Fax: +63 2 5211036
E-mail: ChristophelE@wpro.who.int

Dr Charles Delacollette
Coordinator
WHO/Mekong Malaria Programme
c/o Faculty of Tropical Medicine
Mahidol University
420/6, 7th floor, New Chalermprakiat Building
Ratchawithi Road,10400 Bangkok, Thailand
Tel: +66 (0) 2 643 58 59
Fax: +66 (0) 2 643 5870
Mobile +66 (0) 819111705 (direct)
E-mail: delacollette@searo.who.int

Ms Carol D'Souza
Consultant
21/2 Soi Pipat, Silom Road, Bangrak
Bangkok 10500, Thailand
Tel: +66 (0) 89 508 2057
E-mail: carol.dsouza@bluewin.ch

Dr Juntra Kasbwang
Clinical coordinator
TDR
WHO/HQ

Dr Michael O'Leary
WHO Representative
WHO/Cambodia
E-mail: olearym@cam.wpro.who.int

Dr Pascal Ringwald,
Medical Officer
Anti-malarial Drug Resistance
Global Malaria Programme
WHO/HQ
E-mail: ringwaldp@who.int

Dr Junko Yasuoka
Scientist Malaria
Malaria, Other Vector-borne and
Parasitic diseases,
WHO/Cambodia
E-mail: yasuokaj@cam.wpro.who.int