

Development of a Strategy towards Elimination of *Plasmodium falciparum* Parasites with Altered Response to Artemisinins

*Report of an Informal Consultation
Bangkok, Thailand, 13–14 February 2008*



**World Health
Organization**

South-East Asia Region Western Pacific Region

Development of a Strategy towards Elimination of *Plasmodium falciparum* Parasites with Altered Response to Artemisinins

*Report of an Informal Consultation
Bangkok, Thailand, 13–14 February 2008*



**World Health
Organization**

South-East Asia Region Western Pacific Region

© **World Health Organization 2009**

This document is not issued to the general public, and all rights are reserved by the World Health Organization (WHO). The document may not be reviewed, abstracted, quoted, reproduced or translated, in part or in whole, without the prior written permission of WHO. No part of this document may be stored in a retrieval system or transmitted in any form or by any means – electronic, mechanical or other – without the prior written permission of WHO.

The views expressed in documents by named authors are solely the responsibility of those authors.

Printed in India

Contents

	<i>Page</i>
<i>Acknowledgments</i>	<i>v</i>
<i>Acronyms</i>	<i>vii</i>
1. Background and introduction.....	1
2. Presentations.....	2
2.1 Update on <i>P. falciparum</i> response to artemisinins.....	2
2.2 Case detection and case management strategy.....	4
2.3 Vector control strategy.....	8
2.4 Operational aspects.....	9
3. Group work: Round table discussion.....	12
3.1 Case management.....	12
3.2 Vector control interventions and personal protection measures.....	15
3.3 Mobile and migrant population/Cross-border issues.....	17
3.4 Cross-cutting issues on MDR containment elements: health systems, capacity building, private sector, village workers and volunteers.....	20
4. Final discussion, tentative conclusions and next steps.....	22
References.....	25

Annexes

1. Agenda.....	27
2. Round tables.....	29
3. List of participants.....	47

Acknowledgments

The informal consultation to develop a strategy to contain/eliminate *Plasmodium falciparum* parasites with altered response to artemisinin was held with technical support provided by WHO Headquarters and the WHO regional offices for South-East Asia and the Western Pacific, and was coordinated by the WHO-Mekong Malaria Programme Office in Bangkok. The organizers of the consultation thank all facilitators and participants for their technical inputs and continuous commitment towards the implementation of a Mekong strategy to eliminate *artemisinin tolerant malaria parasites*.

The WHO-Mekong Malaria Programme wishes to acknowledge the financial support from the Bill and Melinda Gates Foundation (BMGF) and the United States Agency for International Development (USAID) to convene this informal consultation.

Acronyms

ADB	Asian Development Bank
ACD	Active case detection
ACT	Artemisinin-based combination therapy
AFRIMS	Armed Forces Research Institute of Medical Sciences
AMFm	Affordable Medicines Facility (malaria)
AMT	Artemisinin monotherapy
AP	Atovaquone + proguanil (coformulated)
ARCCC (ARC3)	Artemisinin “resistance” confirmation, characterization and containment
ASEAN	Association of Southern Asian Nations
ASPYR	Artesunate + pyronaridine (coformulated)
ATMP	Artemisinin tolerant malaria parasites
BCC	Behavioural change communication
BMGF	Bill and Melinda Gates Foundation
BVBD	Bureau of Vector-Borne Diseases, Department of Disease Control, MoPH (Thailand)
CIDA	Canadian International Development Agency
CNM	National Malaria Centre (previously Centre National de Malariologie) in Cambodia
COMBO RDT	RDT which are able to identify <i>P. falciparum</i> and other malaria species infection (e.g. Pf/Pv RDT)
CQ	Chloroquine
DDF	Department of Drugs and Food (Cambodia)
DHA	Dihydroartemisinin

DHAPIP	Dyhydroartemisinin + piperazine (coformulated)
DOTS	Directly observed treatment strategy
EDAT	Early diagnosis and appropriate treatment
EMA	European Medicine Agency
FDA	Food and Drug Administration (United States)
FHI	Family Health International
GSK	GlaxoSmithKline
GF	Global Fund to fight AIDS, TB and Malaria
GFR6	Global Fund round 6 (Cambodia)
G6PD	Glucose 6 phosphate dehydrogenase
GMP	Good manufacturing practice
GMP/HQ	WHO Global Malaria Programme/headquarters
HIS	Health information system (data usually generated by public health-care facilities only)
HU	Health Unlimited
IOM	International Organization for Migration
IRS	Indoor residual spraying
ITN	Insecticide treated bednet
LSHTM	London School of Hygiene and Tropical Medicine
LLINs	Long-lasting insecticidal nets
LLIH	Long-lasting insecticide treated hammock
MDR	Multi drug resistance
MHW	Migrant (community) health worker

MHV	Migrant (community) health volunteer
MMP	WHO-Mekong Malaria Programme (based in Bangkok)
MIMP	Meaningful involvement of mobile population
MTG	Malaria treatment guidelines
MORU	Mahidol Oxford Research Unit
MoH	Ministry of Health
M&E	Monitoring and evaluation
NIMPE	National Institute for Malariaology Parasitology and Entomology (Viet Nam)
NGO	Nongovernmental organization
OD	Operational district (Cambodia)
PFD	Partners for development
PCD	Passive case detection
PCR	Polymerase chain reaction
PCT	Parasite clearance time
Pf	<i>Plasmodium falciparum</i>
<i>Pfmdr1</i>	<i>Plasmodium falciparum</i> multidrug resistance 1 gene
PIP	Piperaquine
PSI	population Services International
Pv	<i>Plasmodium vivax</i>
QA	Quality assurance
QC	Quality control
RDT	Rapid diagnostic test

SCF	Save the Children Funds
TB	Tuberculosis
TICA	Thai International Development Cooperation Agency
TOR	Terms of reference
UNFPA	United Nations Fund for Population Activities
USAID	United States Agency for International Development
USP	United States Pharmacopeia
VC	Vector control
VHV	Village health volunteer
VHW	Village health worker
VMW	Village malaria worker
VHSG	Village health support group (Cambodia)
WB	World Bank
WHO	World Health Organization
WHOPES	WHO pesticide evaluation scheme

1. Background and introduction

Since the 1970s, the border area between Cambodia and Thailand has been the epicentre of emerging resistance of *Plasmodium falciparum* to anti malarial drugs, starting with resistance to chloroquine, followed by resistance to sulfadoxine-pyrimethamine and then to mefloquine.

In response, Cambodia and Thailand have adapted their national malaria treatment policies accordingly. Since 1995, Thailand has been using a two-day course (changed to a three-day course in 2008) of artesunate in combination with mefloquine (loose tablets) plus a single dose of primaquine for the treatment of uncomplicated falciparum malaria in selected provinces where mefloquine resistance has been documented. Cambodia adopted a three-day course of artesunate plus mefloquine (co-packaged) country-wide in 2000.

Results from regular therapeutic efficacy studies conducted in Cambodia and Thailand during the last ten years have demonstrated decreasing sensitivity of *P. falciparum* strains to first-line ACTs (artemisinin-based combination therapies) as well as a dramatic increase in resistance to mefloquine used alone at 25 mg per kilogramme for two days. All current WHO-recommended treatment regimens for managing *P. falciparum* malaria infections are based on artemisinin derivatives. If the increasing ACT failure rates seen in the Mekong region are due to artemisinin resistant *P. falciparum* strains, this would constitute a regional and global emergency, because artemisinin resistance might be expected to follow the pattern seen with resistance to other malaria drugs and spread to other continents, including Africa, where the malaria burden is very high [1,2,3,4].

The informal consultation organized in Phnom Penh, Cambodia, in January 2007 resulted in two key recommendations: (a) to explore underlying reasons for the emergence of drug resistance and to conduct studies in western Cambodia to actually document *P. falciparum* resistance to artemisinins according to a modified and agreed protocol; and (b) to set up and deploy a comprehensive and multisectoral strategy to halt the development and prevent the further spread of malaria drug resistance [5].

The preliminary results of the ensuing in-depth studies conducted in Pailin in Cambodia were presented at an informal consultation in Bangkok on 9 February 2008, as well as preliminary results of studies conducted elsewhere in the Asia region [6]. The common statement that was framed, based on the current yet fragmented information available, was that there is no clear evidence that artemisinin resistance *per se* has emerged and been disseminated. However, by carefully studying important parameters like the parasite clearance time (PCT) over time and space, an increasing number of patients are observed every year with significant slower PCT in western provinces of Cambodia and eastern provinces of Thailand. That evidence is worrisome enough to justify conducting collaborative public health and scientific investigations to confirm and characterize tolerance or resistance and measure its geographical extent [6].

The consultation also outlined the elements of a proposal for an international initiative to intensify efforts to contain or even eliminate multi-drug resistance at the Cambodia-Thailand border. Measures for mobilizing governments, partners and additional funding were discussed.

The follow-on informal consultation described herein aimed to bring experts from different horizons and technical backgrounds together under WHO-MMP coordination to agree on the way forward. Specific objectives were:

- To review the latest evidence pertaining to *P. falciparum* resistance to artemisinins and ACT (including results from the recent therapeutic efficacy studies in Pailin and elsewhere in Asia).
- To develop an achievable strategy for the elimination or containment of artemisinin-tolerant malaria parasites (ATMP) in the region based on up-to-date epidemiological information and on the latest agreed-upon available tools.

2. Presentations

2.1 Update on *P. falciparum* response to artemisinins

Dr Pascal Ringwald gave a presentation which highlighted the following key points:

- A review of data from 2001 to 2006 at the Thailand-Myanmar border showed a significant increase in the proportion of patients failing to clear their parasitaemia by Day 2. Prior to 2001, 95.5% became aparasitaemic within 48 hours, compared to 77.9% between 2001 and 2005. A small but statistically significant decline in efficacy was observed over the years. Over this same period of time, the proportion of infections attributable to parasites with two or more *pfmdr1* copy number also increased.
- On the Cambodian side, the two-day and three-day parasite clearance times in all the sentinel sites using 2001-2007 therapeutic efficacy monitoring results of ACTs shows that 40-60% of cases are still parasitaemic on Day 2 in southwest Cambodia, as compared to less than 10% in the northeast. On Day 3, while 10% are still parasitaemic in the southwest, all patients from the northeast would have cleared. Overall since 2002 in Cambodia, it has been observed approximately 10% treatment failures in the southwest and less than 5% in the northeast.
- The 2007 Pailin study clearly showed parasite clearance times uniformly prolonged in all patients that either received artesunate 2 mg/kg per day for seven days (AS7), or artesunate 4 mg/kg per day over three days plus mefloquine 15 and 10 mg/kg per day on Day 3 and Day 4, respectively. If parasites are fully sensitive to artemisinins, they are cleared in less than 48 hours. However, in the recent study carried out in Pailin in 2007, falciparum parasites in 7 out of a total of 20 patients were cleared beyond 72 hours. This prolonged PCT was also observed in patients from Trat province (on the border with Cambodia) from 2002 to 2007, where an increasing proportion of patients still parasitaemic by Day 2 and Day 3 was observed over the years.
- A consensus statement between experts from the BMGF-sponsored ARC3 meeting on 9 February 2008 in Bangkok was presented as follows:
 - While ACT treatment efficacy remains high in most studies, prolonged parasite clearance times following treatment with some ACTs and artemisinin monotherapy have been observed along the Cambodia-Thailand border. This clinical and parasitological observation might reflect the emergence of *P.*

falciparum tolerance to artemisinins, but other factors have not been ruled out.

- At present there is no clear evidence that *bona fide* artemisinin resistance has emerged and been disseminated, but the evidence is worrisome enough to justify intense investigation. WHO and partners are conducting collaborative public health and scientific investigations to confirm and characterize tolerance and/or resistance and measure its extent.
- Because of the potentially catastrophic consequences of failing to contain emerging tolerance and/or resistance, it is recommended that malaria elimination efforts in the South-East Asia Region initially focus on this area.

Following his presentation Dr Pascal Ringwald clarified that the epicentre of *P. falciparum* strains showing an altered response to ACTs appears to be in Pailin, but that the actual geographical extent of the problem is still not very clear (there is extensive gene flow in Cambodia and outside). It was hoped that the situation would be clarified somewhat during this informal consultation.

The role of other non-genetic factors possibly involved in the development of an altered response was discussed, such as changes in the vector profile resulting from deforestation, pressure from different drugs at various dosages and regimens, falling immunity in the human population and influx of migrants.

The point was made that even in 1993 the efficacy of mefloquine on the Cambodia-Thailand border was low, despite no recorded use of mefloquine during the 1970s. During ensuing discussions, it emerged that in fact the use of mefloquine had been common in Pailin from as early as 1984.

2.2 Case detection and case management strategy

Dr Kamini Mendis presented WHO's recommendations regarding case management developed during the one-day informal consultation organized in Geneva on 19 January 2008. The strategies and implementation details of which were the focus of the informal consultation [7].

The ultimate aim of the management strategy is to eliminate the *P. falciparum* parasite reservoir, with an intermediate goal of containment of *P. falciparum* (a very high degree of control). The primary focus is *P. falciparum* but taking into account *P. vivax*, which is becoming increasingly important in the region.

The strategy focuses on the following technical elements:

- Ensure early and effective cure of all symptomatic infections by passive case detection, including eliminating infective stages of the parasite;
- active case detection by surveillance; and
- detection and complete treatment of asymptomatic parasite/gametocyte carriers by mass screening and application of the DOTS strategy.

Considering that Artesunate (4 mg/day for three days) and Mefloquine (25 mg/kg split over two days) is the first-line treatment in both Cambodia and Thailand, there will need to be a change in antimalarial policy in targeted areas of both countries. It was clarified that the urgency for a change arises NOT just because of poor treatment efficacy in individual patients, but from the perspective of primarily containing the spread of “artemisinin-tolerant malaria parasites”. Strategic operations in affected areas should contain the spread of the parasite gene pool, which encodes the altered response to artemisinins. The obvious advantage in using a non-artemisinin-based combination is to remove artemisinin drug pressure on selection of low responders.

There are three treatment options considered: artesunate plus pyronaridine (ASPYR), dihydroartemisinin plus piperaquine (DHAPIP) and atovaquone plus proguanil (AP), the latest being not considered as a true combination therapy since drug targets in the malaria parasite are linked [8]. All other antimalarial drug combinations are either not available yet, as coformulations, or are still of variable or questionable quality, or are still in Phase II trials. ASPYR, however, will not be available in the market before 2009. Hence, the only immediately available coformulated alternatives are DHAPIP and AP.

The pros and cons of these two drug combinations were further discussed. DHAPIP is a coformulated drug registered in Cambodia (but not

in Thailand) and has already been in use in the public sector for four years in western provinces of Cambodia. It is currently under review by WHO's MTGs and under consideration for EMEA and FDA registration. Although 2001-2003 data from South-East Asia has shown it to be highly effective and well tolerated, a recent unpublished report from Family Health International (FHI) relating to village malaria workers (VMWs) in Pailin in 2007 showed that 50% of cases are still parasitaemic by Day 2 (G. Watt, personal communication).

The long half-life of piperazine increases the risk of parasites developing resistance to that drug. Several publications have reported on the instability of DHA in tropical conditions [4]. AP is the only coformulated non-artemisinin therapy on the WHO list. Its major advantage is that it does not contain an artemisinin and, therefore, theoretically further decreasing artemisinin drug pressure. It is made to Global Malaria Programme standards and has mainly been used for prophylaxis and treatment in travelers in whom tolerance is good and few failures have been reported [9,10]. In Thailand, it has maintained a 98-99% cure rate in two clinical trials conducted in 1996 and 2006 [11]. The main arguments against the use of AP include: 1) resistance to atovaquone is encoded by a single mutation and therefore can emerge very quickly; 2) the drug currently costs around \$50 for each treatment course but this by itself should not deter it from being considered a viable option.

The merits of including a gametocytocidal drug with the proposed drugs described above, especially in addition to AP, were also presented. While ACTs are more effective against transmission than previous antimalarials, they do not totally prevent the development of gametocytes.

There is some evidence that addition of primaquine to ACT improves the removal of gametocytes and reduces transmission. The risk of severe haemolysis in G6PD- deficient patients was discussed since the prevalence of G6PD deficiency is approximately 20% in Cambodia and varies from locations. However, severe haemolysis is very unlikely to occur with a single dose PQ treatment. Therefore, given that the aim is to reduce/interrupt transmission, a single dose of 8 amino-quinoline should be added.

It was also recommended that the use of antimalarials described above be based on a confirmed diagnosis (microscopy and/or RDT) because malaria accounts for only a small proportion of fevers and overuse of antimalarial medicines should be avoided since it is a leading cause of resistance development.

There are two basic types of RDTs available: falciparum-specific and falciparum specific + pan-specific (identifying all malaria species in addition to *P. falciparum*). The only limitation is that the sensitivity to *P. vivax* is currently not more than 80% (not identifying infections with parasite density below 200/ μ l). Data show generally low density parasitaemia in both asymptomatic and symptomatic vivax infections. In recent years the proportion of malaria infections caused by *P. vivax* malaria has grown considerably (probably due to better control of *P. falciparum* malaria) and vivax infection now accounts for around 80% of malaria cases in the border provinces of Pailin and Pursat. Over 80% of confirmed malaria carriers are asymptomatic (Sochantha and Coosemans, unpublished data) [12], which makes the use of Combo RDTs and microscopy or even PCR imperative for mass screening.

The treatment strategy calls for case management to be carried out at all health-care facilities, at the community level through health workers, and through the many (yet unregulated in Cambodia) private providers. Ancillary measures include a highly effective communications strategy for target communities, quality assessment and control of medicines and diagnostics, and quality of care by DOTS. This has broad implications for malaria programmes: retraining of health workers and village malaria workers (VMWs) on the use of new RDTs and new treatment regimens will be required; new IEC materials will need to be developed and implemented; the supply chain system will need strengthening as will quality assessment and control; new M&E measures for case management will be needed; and the private sector will need to be fully engaged and more regulated. To effectively cover both ATMP and sensitive parasites, it is proposed to conduct:

- active case surveillance and case investigation in documented areas that are at high risk and also at risk of re-emergence of transmission
- mass screening (asymptomatic and symptomatic carriers) and DOTS of the entire population in selected target areas every six months at least for a year (two or three times)
- enhanced vector control/personal protection measures in target districts

It was mentioned that the involvement of the private sector is imperative as more than 70% of cases are seen by them and the VMWs in

Pailin and neighbouring provinces in Cambodia. It is not unlikely that “selection pressure” is also created as the result of misuse of RDT and ACT through private sector channels. Some participants suggested that, as part of the containment strategy, artemisinin monotherapies (AMT) should be actively removed from the market (and more specifically from the unregulated private sector) to be more aggressively monitored.

It was emphasized that containment efforts and drug of choice must be coordinated and better harmonized (e.g. similar IEC messages targeting migrants and mobile population) at the two border countries to diminish the selection pressure, as preliminary molecular studies have already shown that there is a lot of gene flow (haplotypes) already identified on both sides of the border.

Concerns were raised regarding the overall approach, from containment to elimination. The risk of selecting resistant parasites rather than eliminating them was highlighted. Elimination efforts could either lead to the complete elimination of parasites or to complete elimination of susceptible parasites. The group was urged not to use ACT as the only drug and to consider strategies which are not creating opportunities for susceptible parasites to remain untreated (e.g. by avoiding mass treatment and thereby leaving asymptomatic cases untreated).

2.3 Vector control strategy

Prof. Marc Coosemans gave a presentation reviewing the latest vector control tools in the context of malaria control in western Cambodia. The presentation gave a comprehensive overview of vector biology in the target area (covering geographical distribution, behaviour and insecticide resistance profiles, as well as the results of vector incrimination studies) and of human-vector interactions and the effects of these interactions on the local epidemiology of malaria [12, 13]. Options for vector control and personal protection were discussed. The session highlighted the following key points:

- A large proportion of people with malaria parasitaemia in the target area are asymptomatic carriers. The majority of infections are due to *P. vivax* with a parasitological index from 1.06 to 12.96% and few due to *P. falciparum* from 0 to 1.69%.

- The incidence of malaria in the target areas is highest among adult males and this is linked to this group's involvement in forest-based activities.
- Insecticide-treated hammock nets provide effective protection against vectors in some circumstances, and probably provide the best option for those involved in forest-based activities, as well as to protect villagers during the evening when sitting outside.
- LLINs provide protection late at night but a significant proportion of biting by vectors occurs in the early evening before people are sleeping under their nets. Therefore additional measures should be taken to protect at risk people during evening.
- With some minor modifications (spraying outdoors as well as indoors) IRS could be a useful adjunct to LLINs in selected areas, but pyrethroids should not be used because this could lead to increasing vector resistance to pyrethroids and seriously jeopardize the future effectiveness of LLINs.
- Repellents might be usefully employed to protect people in the early evening. The efficacy of certain insect repellents is well known but additional operational research is needed to investigate the cost-effectiveness of repellents in the field.

During discussions following the presentation it was clarified that deforestation results (a) in the complete disappearance of *Anopheles dirus*, but not *An. minimus* populations (the two primary vectors of malaria in the Region) and (b) subsequent colonization by *An. maculatus* and *An. barbirostris* (much less efficient secondary vectors, which are abundant in many malaria-free areas in the Region).

In parts of Pursat in Cambodia where patches of forest remain, *An. dirus* is locally abundant. In Pailin, as the result of severe deforestation, *An. dirus* is less abundant but *An. minimus* does persist.

2.4 Operational aspects

Dr Eva Christophel gave a presentation describing key operational issues relating to the containment of artemisinin-tolerant parasites in the Region. Delineation of target areas and quantification of target populations for each

of the possible interventions were discussed. The particular difficulties associated with malaria control for mobile populations (including forest workers, internal and cross-border migrants) were highlighted. An overview of public, NGO and both regulated and unregulated private sector health services in the likely target areas of Cambodia and Thailand was presented. Options for the management of the initiative at country and at regional level were discussed, along with likely timing of the various interventions and options for funding. The following key points were made:

- Asymptomatic cases are common and so elimination and perhaps even containment will require mass screening of the target population.
- Public health services and infrastructure generally are particularly weak in the former Khmer Rouge strongholds of Pailin and Pursat which only came under government control relatively recently.
- Cambodia's Health Sector Support Project has identified this area for infrastructure development in 2008, but resulting improvements in coverage of public sector health care provision will take time.
- Rapid scale up of containment activities will require major scale up of NGO and community involvement.
- Only after clear strategies have been defined can an operational plan be developed and a detailed programmatic and financial gap analysis carried out.

During discussions following the presentation, it was noted that public sector passive case detection appears to be missing many *P. vivax* infections (a much higher proportion of malaria cases were caused by *P. vivax* in data from NGO-run outreach activities) in a context where more than 70%¹ of patients in Cambodia seek their malaria treatment in private facilities [14]. Whether among many hypotheses this is because people with vivax malaria feel less ill and so are less inclined to seek treatment, or because the treatment that they seek from the private sector is more convenient for them or because diagnostic tools are not available or too expensive is unclear yet.

¹ Preliminary results from the Cambodian national malaria survey conducted in November 2007 demonstrate that around 60% of patients are seeking care from private providers (nationwide)

It was pointed out that the impact of the current social marketing programme is rather limited: the ACT that it provides tends not to penetrate the market beyond the district centre level, and RDTs marketed at low cost are not popular. It was surmised that this was due in part to the relatively high price of the products and in part to the choice of drug combination used (artesunate plus mefloquine). The unpleasant side effects associated with therapeutic doses of mefloquine are well known in Cambodia and there are reports from the field of patients using only the artesunate tablets from the marketed Malarine® treatment through PSI and discarding the mefloquine (the drugs are presently copackaged and not coformulated).

Some suggested that more emphasis should be placed on strengthening the performance of the public sector rather than the private sector. Others felt that the performance of the private sector could be strengthened (with increasing regulation and monitoring of private practices) by focusing more on training providers on the provision of appropriate treatment. The overall consensus was that both public and private sector delivery should be strengthened.

The fact that 25% of migrant workers on the Thai side of the border with Cambodia are from Myanmar raised strong concerns. It was suggested that any containment operation focussing exclusively on the Cambodia-Thailand border would be fundamentally flawed because of the high risk of spread of tolerant parasites to Myanmar. It was pointed out that the tolerant parasites might already be in Myanmar. It was agreed that Myanmar must be engaged in the containment process as soon as possible.

With 700 000 people at risk of malaria in the seven provinces of Cambodia where the risk of development of resistance to ACT is considered to be highest, it was agreed that the task of containment was a major undertaking. Doubts were expressed regarding the suitability of PCR for screening. It was suggested that PCR should instead be used selectively for operational research such as mapping gene flow in the target areas.

There was a call for more public-private cooperation and for more collaboration with other sectors outside health (particularly relevant in the case of mobile populations and migrants).

It was pointed out that the coverage of public sector health facilities is still limited in Cambodia and not well suited to providing care for mobile populations.

In the west of Cambodia, the prevalence of vivax malaria is much higher than that of falciparum malaria (see above). Furthermore, as already mentioned, malaria accounts for only a small proportion of fever cases. A question was raised regarding the groups ethical position on treating these non-falciparum cases during mass screening activities. It was agreed that all vivax malaria cases should be treated but that other cases should be referred to the nearest health facility for follow-up.

3. Group work: Round table discussion

3.1 Case management

The working group dealing with case management gave a presentation of the specific implementation strategies agreed upon by the two countries,

The following impact level indicators were suggested:

- (1) Reduce overall incidence of *P. falciparum* to less than 5 per 1000 of the at-risk population (pre-elimination malaria threshold level refers to SPR in symptomatic cases to be less than 5% during 3 consecutive years) [15];
- (2) Reduce prevalence of *P. falciparum* in sentinel sites to less than 1%;
- (3) Reduce overall incidence of malaria (Pf and Pv) to less than 10 per 1000 (yet to be decided) in the target areas, bearing in mind that Pf/Pv ratio in that region is less than 20%, which deserves the development of a clear, do-able strategy to manage *P. vivax* cases to avoid recrudescence from hypnozoites.

The following methods can be used to produce the above indicators:

- Data generated by the HIS (taking into account potential inaccuracies, e.g. because of the expected increased use of public health facilities resulting in an apparent increase in incidence)
- Cross-sectional prevalence surveys (e.g. parasite and spleen index) in sentinel sites
- COMBO RDT positivity rate or SPR generated at village level (e.g. by VMWs)

The following key points were made:

- DHAPIP in Cambodia and AP in Thailand were seen to be the treatment of choice in the public sector (both in health-care facilities, in malaria posts and by VMWs).
- Mass screening/ACD should be carried out twice a year (before and after rainy season) using Pf/Pv RDTs + microscopy, possibly PCR and AP with primaquine single dose (30 mg or 0.50-0.75 mg/kg). Routine monitoring through identification of molecular markers (e.g. Cytochrome b) to detect early resistance to AP to be introduced in both countries.
- DOTS to be implemented in target districts by VMWs in Cambodia and by malaria clinic workers in Thailand.
- *P. vivax* treatment to be with CQ (and referral for 14-day PQ treatment with G6PD screening).
- Thailand can carry out a 28-day follow-up of patients through mobile teams/village malaria workers/volunteers. Cambodia can carry out such follow-up through cohort population surveys as an operational research study yet to be finalised.
- Duration: one year (initially).
- Implementation areas have been selected as follows:
 - Thailand: Pong Nam Ron and Soi Dao districts in Chanthaburi province, and Bo Rai district in Trat province (approximately 600 Pf and 1400 Pv cases are recorded per year).
 - Cambodia: Pailin province, Samlot and Sampouv Loun districts in Battambang province.
- Communication strategy to be developed and scaled up for mobilizing people with malaria symptoms.
- Operational research to include the characterization of parasites (through the Gates ARC3 research grant) and mapping of artesunate-tolerant parasites in Cambodia and the Region (partially started with Gates ARC3 and USAID funds).
- Operational research studies in case management are needed for:

- *in vivo* AP safety and efficacy in Cambodia
- *in vivo* DHAPIP and *in vitro* sensitivity of piperazine in Cambodia
- G6PD deficiency phenotypes/genotypes in both countries
- screening for cytochrome *b* mutation to monitor the evolution of AP resistance

Regarding a time frame for implementation, it was reiterated that the proposal will have to be submitted and approved first by the Ethics Committees in both countries. AP is registered in Thailand, but not yet in Cambodia. DHA-PIP is registered and already used in Cambodia but not in Thailand. Both countries must start with the preparatory procedures as soon as possible, so field implementation can start in June before the onset of the rainy season. To allay fears that resistance to AP may emerge, it was clarified that AP will be used only in the mass screening operations in Cambodia and be given only once to identified *falciparum* positive patients. DHAPIP will still be available at the private sector and the public health facilities for routine PCD in case of re-infection and treatment failure. Another issue raised was the need to explain these different treatment regimens to the community at large. In Thailand, VBDC suggested that AP be made available in the public health facilities and malaria posts of the three target districts as first-line treatment. ACD is done regularly by provincial malaria teams as part of routine case investigation at village level. However, VBDC will need to hire more village malaria workers to perform the 3-day DOTS and active 28-day follow-up.

WHO headquarters will negotiate with GSK the possibility of a few thousands doses of AP to be available to Thailand and Cambodia. This drug will be for restricted use only in this “emergency situation”.

The Cambodia programme manager also mentioned that the public health facilities will waive user fees to attract more patients from the private sector services. CNME will mobilize its provincial teams to conduct the mass screenings together with village malaria workers. More VMWs will be hired and trained in target areas to assist in the mass screening and diagnosis/treatment of cases. The program plans to strengthen routine microscopy with inclusion of quality assurance in both microscopy and RDT use.

3.2 Vector control interventions and personal protection measures

The working group dealing with vector control and personal protection gave a presentation which highlighted the following key points:

- For the main vectors, most (but not all) biting occurs after 10:00 pm and therefore bednets can clearly be protective.
- Although the majority of people do sleep under nets, most of them are not treated. Therefore the situation requires a combination of free distribution of ample numbers of long-lasting insecticidal nets (LLINs), combined with simultaneous retreatment of existing nets, preferably using a wash-resistant insecticide treatment (long lasting insecticide for retreatment).
- The programme should provide free hammocks and nets treated with long-lasting insecticide to adult males in target areas in an effort to achieve complete coverage of the forest worker population.
- In selected target areas, houses should be sprayed inside and out with residual insecticides (not pyrethroids however, as this is the only group of insecticide currently available for use on bed-nets and so pressure for selection of resistant mosquitoes needs to be minimized). This service should be provided as well as, and not instead of, LLINs.

Following the group presentation, a number of issues were raised and points clarified.

There was a suggestion that insecticide-treated nets (ITN) coverage should be increased to the level of one net per person (sourced from the Global Fund, World Bank and national budgets). In response, Jo Lines (the London School of Hygiene and Tropical Medicine-LSHTM) presented the results of a study demonstrating that coverage (proportion of people sleeping under a net) reached 90 percent when household person per net ratios reached around 3.5:1 and was not improved as the number of people per bednet fell (wealthier families tend to have more nets and spread out more, while poorer families share their nets with several family members) [Jo Lines, personal communication]. Another study will be required to identify the level of coverage needed to enable mobile family members to take nets with

them while travelling and still maintain high overall coverage. Unpublished data describing who takes bed-nets or hammock nets to the forest (and majority do) is already available. What needs to be further investigated is why some do not. It may be due to poverty, in which case MoH could provide a solution in the form of free nets; or it may be that the activity being carried out precludes the use of nets (such as hunting), in which case alternative approaches could perhaps be developed.

It was agreed that indoor residual spraying (IRS) with insecticide should be used as an adjunct to LLINs in selected high-risk areas (the criteria for targeting this IRS needs further discussion). It was also agreed that this spraying should in fact not be just indoors (the conventional approach) but also on the outer walls of houses. This modification to IRS takes into account the pre- and post-feeding resting behaviour of local vectors, which are otherwise largely exophilic. It was pointed out that IRS is likely to be particularly effective in houses made of wood (as many in the target districts are) as the insecticide has a longer residual efficacy on wood than on other materials used for house construction in the Region.

It was agreed that net-based interventions should target the entire population in the target districts. It was further agreed that the target should be to have 100 % of people sleeping under an LLIN.

Almost all of the bed-nets destined for Cambodia pass through the Olympic Market in Phnom Penh. It was suggested that by setting up a net treatment facility at the market, it would be possible to ensure that all private sector nets coming into the country are LLINs. This might take more than a year. In the meantime, bed-net distribution teams should provide free dipping of all non-long-lasting nets using long-lasting insecticide for retreating nets currently approved by the WHO Pesticide Evaluation Scheme) [16].

It was suggested that the private sector could be used to target any newcomers (including migrant workers) arriving in target districts.

The group was informed that further investigations will be needed on repellents to measure efficacy and if possible effectiveness under real-life conditions. Some studies have been carried out by the National Institute for Malaria Parasitology and Entomology (NIMPE) in Vietnam, but the results of these have not yet been published. This work should be reviewed when possible. Further research is also needed to develop personal protective

measures for those spending time working in the forest at night such as rubber plantation workers, police and soldiers. It was agreed that repellents and/or impregnation of clothes or blankets were likely to result in some diversion of mosquitoes from users to non-users, but that this would be limited and the overall impact of such measures was likely to be protective.

It was agreed that the quantification of needs will require additional rapid field assessments as at present there is limited up-to-date information on bednet coverage in communities further than one kilometre from the forest (bearing in mind that bed-net coverage does not fully correlate with the distance from the forest). Bed-net ownership is likely to be high, particularly in rice growing areas where biting by nuisance mosquitoes is often intense. Due to accelerated effort by the national malaria programme, there is increasing use of bed-nets provided free of charge by the MoH in villages less than one kilometre from the forest.

3.3 Mobile and migrant population/Cross-border issues

The working group dealing with mobile and migrant population and cross-border issues gave a presentation that highlighted the following key points:

- Definition and magnitude of the migratory patterns is still a big question. Mobile populations move from one place to another, either temporarily, seasonally or permanently, for either voluntary or involuntary reasons. It is a broad category including the full range of mobility, from short-term movement (e.g. truck drivers) to longer-term or permanent relocation. "Migrant" is a more specific term that is used for those mobile people who take up residence or remain in another location for an extended period of time, including seasonal migrations. Internal migrants move from their homes to other places within the same country. External migrants are people who cross international borders and live in another country [17]. Those definitions can be slightly modified for specific communicable disease programme targets such as malaria to support proactive case investigation (e.g. prevention of re-introduction of malaria). For example in Thailand, BVBD classifies people who stay in one place for not more than three months as M2 (highly mobile and difficult to trace) and those staying in one place for more than three months as M1 (mostly residents).

- Knowledge is sparse regarding the number of migrants, where they came from and where they are going, both within and between countries (Cambodia to Thailand, Thailand from west to east, Cambodia from north to south, etc.). Thailand reported 1020 confirmed malaria cases amongst foreigners in 2007 in seven provinces along the Cambodia-Thailand border, but there are significant numbers on the Thai-Myanmar border as well.
- There is a need for increased boundary border surveillance and active investigation, apart from the six official immigration check points. Screening posts on both sides need to be set up for people crossing the border. This should concentrate on zones where malaria is present and identify high-risk groups.
- Some mobile population goes to the private sector and the question arises as to how to collect information on these patients. There will be a need to involve local authorities and private providers as well.
- Cambodia has passive case detection (PCD) in public health facilities. Where there is a lack of health centres, VHW are posted in villages to provide diagnosis (RDT) and treatment.
- Thailand has developed comprehensive forms and systems to report confirmed malaria cases in Thai and non-Thai citizens with several subgroups according to their civil status (e.g. some long-term residents are not recognized as Thai citizen like ethnic minority people). Cambodia can develop a surveillance report system based on Thai forms towards a common multicountry data base.
- Regulations and policy in Cambodia and Thailand for migrants are different and continuously evolving, e.g. pertaining to free access or not to health care services.
- Cambodia would focus on internal migration while Thailand would focus on cross-border investigations. But they would need to link their activities to ensure both internal and cross-border migration is addressed.
- Establish and harmonize cross-border activities with a multisectoral approach with involvement of ministries from health, interior, defense, foreign affairs and labor.

In the ensuing discussions, it was pointed out that a major problem with “undocumented” or “unrecorded” migrants is that they do not seek medical services in any of the official health facilities in Thailand, for fear of reprisal and deportation. Some local factories and plantations hire these migrant workers; hence there is a need for the programme to coordinate with factory/plantation owners and the office of migration for better documentation and reporting of malaria cases. Cross-border movement has always been a complex issue in Cambodia in the 1980s and the 1990s during the height of the gem mining years, and more so now with renewed economic activities and rapidly growing open road network initiated after the peace process of 2003.

There are six official check points, but there are of course more “unofficial” entry points, which may necessitate additional malaria screening posts. Migrant volunteers can be trained for volunteer health services recognized by both the Thai and Cambodian authorities. On the Thai side, it was pointed out that some NGOs like CIDA and UNFPA have organized trainings and are now working with migrant volunteers on TB and AIDS/HIV. A similar approach can be done for malaria diagnosis and treatment. It was suggested that they can be involved even in the proposed mass screenings, follow-up and IEC of patients and the communities at large. This is referred to as meaningful involvement of mobile populations (MIMP) as “peer educators”, documented in a recent publication of FHI/USAID “Protecting People on the Move” [17]. It has been noted that the Thai International Development Cooperation Agency (TICA) is regularly providing funds to provinces and/or districts to support cross-border projects by strengthening collaborative efforts with neighbouring country provinces to Thailand e.g. increasingly looking at improving health status of migrants.

It was also pointed out that the migrant population is a very heterogenous group with various backgrounds and some with potential to be used as health volunteers or workers. To capture information needed both sides e.g. to capture origin of infections, there is a need to harmonize surveillance systems across the border. In Thailand, aside from other health services, some malaria posts are manned by migrants now. The project can train the same people to participate in the active case surveillance, since they are in a better position to understand (because of cross-cultural and language skills) and approach their fellow migrants in the same village.

The International Organization for Migration (IOM) is currently active on the Thai side of the Thai-Myanmar border. They proposed to organize a system to ensure that migrants are fully part in the “containment activity”, but they cannot do much on the other side of the border.

It was also proposed to raise this issue on the health of the migrant population with ASEAN or other multicountry forum, as part of the long-term effort to bridge migrant people into better health throughout the Region.

3.4 Cross-cutting issues on MDR containment elements: health systems, capacity building, private sector, village workers and volunteers

The working group dealing with cross-cutting issues gave a presentation that highlighted the following key points:

- The Affordable Medicines Facility (malaria) [AMFm] initiative should be approached to initiate activities in the Mekong Region.
- In Cambodia, subsidized ACTs and free RDTs should be provided to the private sector following the AMFm approach. This cannot wait for the launch of AMFm. The first steps should be taken immediately. Population Services International is probably best placed to take the lead.
- In target districts, private sector ACT and RDT requirements need to be quantified through a rapid assessment of stocks at a representative sample of wholesalers, pharmacies and other drug outlets. Requirements must not be underestimated and it is crucial that stock-outs are avoided.
- A ban on the import of artemisinin monotherapies should be imposed in Cambodia.
- Cambodia’s VMW scheme should be expanded to provide complete coverage of communities in target districts. In order to strengthen performance, the volunteers should be provided with realistic financial and other incentives and against updated terms of reference (TORs).

- The public sector microscopy network will be strengthened with support from the sixth round of the Global Fund.
- Further strengthening of public sector health-care providers should be carried out in target districts through integrated training and supportive supervision.

A number of issues were discussed following the group's presentation.

In order to improve rationale use of antimalarials in the private sector, it was suggested that the social marketing programme might somehow insist on a positive RDT test prior to treatment. A number of people raised concerns that this might be very hard to enforce. The general consensus was that the social marketing approach should use existing private sector mechanisms to influence provider practice rather than dictate terms and conditions. It was agreed that by providing free RDTs alongside the subsidized ACTs and by implementing vigorous IEC/BCC activities targeting both providers and the general public, it should be possible to greatly increase the use of diagnostic tests e.g. by starting operations in the accredited private sector.

MORU raised the idea of exchanging AMTs for ACTs as a means of accelerating penetration of ACTs into the private sector.

Information relating to the AMFm was clarified. The initiative is unlikely to be launched in Cambodia before 2009. When and if it does, it will provide a list of GMP/WHO pre-qualified drugs that it can support. Based on local considerations, MoH will be able to decide which drugs from this list to use.

It was pointed out by some members of the group that a lot of political groundwork will probably be needed before a ban on the import of antimalarials (and a ban on the sale of any illegal imports) can be effectively policed.

The group agreed that care will be needed during the design of the initiative's M&E plan to ensure that those who are implementing the project are not expected to self-assess, but are monitored by a suitably qualified third-party group.

There was some discussion of the type of RDT best suited to the needs of the containment project. The consensus was that combination tests

should be used in conjunction with microscopy for cross-checking negative slides (the sensitivity of the pan-specific component of combination RDTs is currently less than 80%). Although somewhat cumbersome, it was agreed that this option is the best available at present.

It was agreed to incorporate one day primaquine (see dosage in group A section above) into the treatment regimen administered by VMWs and health-care providers.

The history of the development of the Thai malaria treatment network was discussed. In Thailand, the malaria clinics are similar in function to the volunteers engaged in the Cambodian VMW scheme which will be expanded under this initiative. In Thailand, rather than simply legislate against unregistered health-care providers, the MoH developed a facility to allow their children to be trained in pharmacy at government colleges without the need for entrance exams. This type of approach might work well in Cambodia and help to maintain unregulated private practices out of business.

4. Final discussion, tentative conclusions and next steps

At the end of the meeting a presentation summarizing the key points and identifying areas for further clarification was reviewed in plenary.

A consensus was reached that in Cambodia, the MoH should follow the example set by the National TB Programme and should ban the importation of antimalarials by the private sector. The director of the Cambodian Department for Drugs and Food (DDF) explained that penalties could be imposed on violators of the ban and that the department would take responsibility for enforcement and for tracking counterfeits in association with CNM and USP (currently conducting drug quality monitoring using MiniLabs[®] test kit under the sixth round of the Global Fund).

In order to encourage reliance on the public sector it was proposed that all user fees associated with the diagnosis and treatment of malaria should be waived.

It was agreed that further strengthening of the public sector supply system would be required and that safeguards would need to be put in place

to mitigate the risk of supply problems at central level. Given the scale of the preparation likely to be required it was agreed that introduction of the ban would not be possible until 2009 at the earliest. It was also agreed that because of the acute nature of malaria infections and given the current limited coverage of the public sector network (notwithstanding proposed expansion of the VMW network), it would be unwise to rely exclusively on the public sector to provide EDAT. It was agreed that the supply of antimalarials to the private sector would need to be maintained using social marketing channels, for example. Strengthening of existing social marketing channels and lowering the price of socially marketed antimalarials would be needed to ensure effective supply to all private sector drug sellers (including those in remote periphery).

It was suggested that the pilot project currently being planned by MORU in association with the CNM should follow the lines of this new approach.

The following key points for immediate action were identified:

- WHO headquarters contact the GSK company regarding AP procurement/donation and clarification of treatment guidelines for small children².
- Studies should be carried out to investigate the interactions of ACTs and/or AP with primaquine³.
- A project proposal will need to be written and submitted for ethical review in Thailand and Cambodia.
- An estimate of existing coverage of conventional bed nets, LLINs and hammock nets in the target areas is needed to quantify project requirements.
- Updated training materials need to be prepared.

² Aside from the adult tablets, paediatric tablets with atovaquone 62.5 mg and proguanil 25 mg exist with dosing down to 5kg weight. A rigorous driven AP Donation Programme in Kenya in 1996 provided outstanding insights pertaining to the use of AP under DOT based on strict criteria e.g. targeting those patients not responding to the first-line sulfadoxine-pyrimethamine (a total of 1101 patients were on AP out of 161079 clinically diagnosed). There was no in vivo and in vitro resistance to AP observed, with four cases showing minor side effects such as stomach cramps, nausea and vomiting [18].

³ There are two investigator-driven studies available so far. One in vitro study demonstrated that primaquine is not a good choice for combination with atovaquone [19]; another clinical study shows the sequential administration of atovaquone-proguanil® and primaquine in *P. vivax* patients was safe and effective [20].

- The AMFm should be lobbied to initiate its activities in the Greater Mekong Sub-region (GMS) as soon as possible and to accelerate access of recognized private providers to subsidized ACTs.

Inadequate pay is one of the key factors identified during the consultation that undermines the effectiveness of the public sector in general. Future containment proposals have to focus on human resources and skills and incorporate salary incentives as part of the health system strengthening component.

Next steps:

The following key issues were identified for further discussion at the stakeholders' meeting in Phnom Penh planned from 25 March, 2008:

- Initiate operational planning for 2008 and beyond (based on the strategy developed during this meeting);
- coordinate partners' activities and budgets;
- identify intervention and funding gaps in targeted provinces with involvement of provincial teams and NGOs; and
- mobilize funds against funding gaps yet to be urgently identified.

Among future milestones to be considered is the set up of agreed-upon managerial structures of the short- and long-term containment operations. No final consensus was reached due to time constraints, but it was suggested to create an international task force chaired by GMP/WHO headquarters including regional offices backing up national task forces in Cambodia, Myanmar and Thailand. It was suggested (and yet to be formalized) to set up several *ad hoc* technical committees in the following technical areas: (1) geographical and demographic (exchange of) information; (2) research; (3) case management; (4) private sector; (5) VC and personal protection; (6) mobile population and migrants; (7) Health System strengthening; (8) monitoring and evaluation; and (9) resource mobilization and advocacy.

References

- (1) Roper C, Pearce R, Nair S, Sharp B, Nosten F, Anderson T. Intercontinental spread of pyrimethamine-resistant malaria. *Science*. 2004 Aug 20;305(5687):1124.
- (2) Hasting I.M. The origin of antimalarial drugs resistance. *Trends in Parasitology*, vol 20, 11, November 2004
- (3) Anderson TJC and Roper C. The origins and spread of antimalarial drug resistance: lessons for policy makers. *Acta Tropica*, 94,(2005), 269-280.
- (4) White NJ. Qinghaosu (Artemisinin): The Price of Success, a review. *Science*, Vol. 320, April 18, 2008, #5874, 330 - 334
- (5) 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
- (6) WHO: Artemisinin Drug Resistance: Confirmation, characterization and containment: Report of an informal consultation, Bangkok, Thailand, 9 February 2008
- (7) WHO: Global malaria control and elimination: Containment of artemisinin resistance at the Cambodia-Thailand border: Report of an informal consultation, Geneva, Switzerland, 19 January 2008.
- (8) WHO: Guidelines for the treatment of malaria. WHO/HTM/MAL/2006.1108 ISBN 92 4 154694 8.
- (9) Boggild AK, Parise ME, Lewis LS, Kain KC. Atovaquone-proguanil: report from the CDC expert meeting on malaria chemoprophylaxis (II). *AM J Trop Med Hyg*, Feb 2007; 76 (2): 208-23.
- (10) Nakato H, Viraneos R, Hunter P. A systematic review and meta-analysis of the effectiveness and safety of atovaquone proguanil (Atovaquone-proguanil) for chemoprophylaxis against malaria. *J Antimicrob Chemother*, Nov 2007; 60 (5): 929-36.
- (11) Krudsood S, Patel S, Tangpukdee N, Thanachartwet W, Leowattana W, Pornpininworaky K, Boggild A, Looareesuwan S and Kain K. Efficacy of Atovaquone-Proguanil for treatment of acute multi-drug resistant Plasmodium falciparum in Thailand. *AM J Trop Med Hyg*, 2007; 76 (4): 655-658.
- (12) Trung HD, Bortel WV, Sochantha T, Keokenchanh K, Quang LT, Kong LD and Coosemans M. Malaria transmission and major malaria vectors in different geographical areas of South East Asia. *Tropical Medicine and International Health* , 2004; 9: 230-237.

- (13) Trung HD, Van Bortel W, Sochantha T, Keokenchanh K, Briet O and Coosemans M. Behavioural heterogeneity of Anopheles species in ecologically different localities in Southeast Asia: a challenge for vector control. *Tropical Medicine and International Health*, 2005;10:251-262
- (14) CNM, RPM+, EC Cambodia, WHO and Wellcome Trust Mahidol-Oxford: Community drug use practices in malaria in Cambodia: a cross-sectional study, final draft report, March 2003, 108 pages
- (15) WHO: Malaria elimination: A field manual for low and moderate endemic countries. 2007. ISBN 978 92 4 159608 4
- (16) WHO – Review of Spinosad 7.48% DT, Netprotect®, Duranet®, Dawaplus®, Icon® max. [Report of the 11th WHOPES Working Group meeting](#), 10-13 December 2007, Geneva. WHO/HTM/NTD/WHOPES/2008.1
- (17) FHI/USAID “Protecting people on the move”: Applying lessons learned in Asia to improve HIV/AIDS interventions for mobile people. 2006. ISBN 974-94322-6-6
- (18) Olukayode Oyediran ABO, Ddumba EM, Ochola SA, Lucas AO, Koporc K. & Dowdle WR. A public-private partnership for malaria control: lessons from the Atovaquone-proguanil Donation Programme. *Bull. of the WHO*, 2002, 80 (10), 817-821.
- (19) Canfield CJ, Pudney M. and Gutteridge WE. Interactions of Atovaquone with other antimalarial drugs against *P. falciparum* in vitro. *Experim. Parasitology*, 1995, 80, 373-381
- (20) Looareesuwan S., Wilairatana P., Glanarongran R., Indravijit KA., Supeeranontha L., Chinnapha S., Scott TR., Chulay JD. Atovaquone and proguanil hydrochloride followed by primaquine for treatment of *Plasmodium vivax* malaria in Thailand. *Trans. Roy. Soc. Trop. Med. Hyg.*, 1999, 93, 637-640.

Annex 1

Agenda

Wednesday 13th February

08.00–09.00	Registration of participants	
09.00–09.20	Introductory remarks: Meeting background and objectives Designation of chair and rapporteurs	<i>C. Delacollette</i>
09.20–09.40	Update on <i>P. falciparum</i> response to artemisinins	<i>P. Ringwald</i>
09.40–10.00	Points for Clarification	
10.00–10.20	Case detection and case management strategy	<i>K. Mendis</i>
10.20–10.40	Points for Clarification	
11.05–11.25	Vector Control Strategy	<i>M. Coosemans / P. Guillet</i>
11.25–11.45	Points for clarification	
11.45–12.10	Operational aspects health service infrastructure (incl. private sector), community infrastructure (CHWs, acceptability) migrant populations	<i>E. Christophel</i>
12.10–12.30	Points for clarification	
12.30–14.00	Lunch at Patummat Restaurant (1 st Floor)	
14.00–14.20	Introduction to round table group work	<i>C. Delacollette</i>
14.20–18.00	Group work to finalize containment / elimination strategy	
16.30–18.00	Group work to finalize containment / elimination strategy (cont'd)	

Thursday 14th February

08.30–10.15	Group work to finalize containment / elimination strategy (cont'd)	
10.30–10.45	Group work on finalizing containment / elimination strategy (cont'd)	
10.45–12.30	Plenary - working groups report back + discussion	

12.30–12.45	Group work to define / develop main activities (according to strategic components defined above) and indicators of an operational plan to contain / eliminate falciparum parasites with altered response to artemisinins	<i>C. Delacollette</i>
12.45–14.00	Lunch at Patummat Restaurant (1 st Floor)	
14.00–16.00	Group work on operational plan for implementation	
16.15–17.30	Plenary - working groups report back	
17.30–18.00	Next Steps Discussion and declaration of commitments by stakeholders	<i>E. Christophel</i>
18.00	Concluding Remarks	<i>J. Ehrenberg</i>

Annex 2

Round tables

Overall Goal: To contain the spread of *artemisinin-tolerant malaria parasites* by reducing and ultimately eliminating *P. falciparum* malaria

Round Table A. Case management as part of containment operations

Strategic technical elements to consider	To be implemented in Cambodia	To be implemented in Thailand	Research gaps	Action points to consider
A.1. ACT or non-ACT treatment?	<ul style="list-style-type: none"> – DHAPIP to be used in the public and private sector in routine passive case detection 	<ul style="list-style-type: none"> – AP to be used in public health facilities of Borai district (in Trat province) and Pongnamron, Soi Dao districts (in Chantaburi province), as a "research drug", for one year 	<ul style="list-style-type: none"> – In vivo efficacy and safety of AP with and without primaquine 	<ul style="list-style-type: none"> – Need to discuss supply of drugs with GSK
	<ul style="list-style-type: none"> – AP to treat symptomatic and asymptomatic cases detected in ACD and mass screening 	<ul style="list-style-type: none"> – AP to treat symptomatic and asymptomatic cases detected through PCD and ACD 	<ul style="list-style-type: none"> – Screening for cytochrome B mutation to monitor atovaquone-proguanil resistance 	<ul style="list-style-type: none"> – Back up for atovaquone-proguanil available first-line drug
	<ul style="list-style-type: none"> – As a "village-based clinical trial drug" for one year; requires ethics committee approval and drug regulatory requirements 	<ul style="list-style-type: none"> – AP is registered in Thailand, but National Malaria Committee endorsement and MoPH approval is required 	<ul style="list-style-type: none"> – In vivo and in vitro efficacy of piperazine 	
A.2.1. Primaquine single dose in addition to ACT and AP for Pf?	<ul style="list-style-type: none"> – Primaquine single dose 30mg for Pf cases (0.5-0.75mg/kg for kids) in public, private HC and in villages with VMWs 	<ul style="list-style-type: none"> – Primaquine 2 tabs (30 mg) currently recommended and used as single-dose standard treatment for Pf in addition to ACT in all health facilities 	<ul style="list-style-type: none"> – Need for day7 drug levels in subset of population (as treatment failures may be due to low drug levels) 	
A.2.2. Primaquine	<ul style="list-style-type: none"> – CQ3d to be administered in 	<ul style="list-style-type: none"> – CQ3d+PQ14d (15 mg base) is standard 	<ul style="list-style-type: none"> – G6PD genotype mapping (as part 	<ul style="list-style-type: none"> – Adherence to PQ14d to be

15 mg (1 tab) x 14 days for Pv	public sector and by VMWs in target area — primaquine is not used — Establish a system of referral of patient to health facility for G6PD screening and 14-day primaquine treatment	treatment for Pv in public health facilities — Send blood from malaria post to HC for G6PD screening	of screening intervention)	investigated and strengthened
A.3. Direct Observed Treatment strategy (DOTs)	— DOTS (for Pf) three days by VMWs and VHV's	— DOTS for three days by health workers/volunteers		Evaluation of DOTS
A.4. Proactive follow-up after PCD	— 28 days (need incentive for those under follow-up)	— 28 days (need incentive for those under follow- up)		
A.5. Diagnostic tools	— Microscopy in existing health centres and RDTs — Train more VMWs on combo RDT (Pf/Pv) use: cooler box storage in remote areas and QA	— Microscopy in existing malaria detection posts — Train health workers on combo RDT use and strengthen QA of RDTs		QC/QA microscopy Training package to be updated
A.5. Mass screening				
A.5.1. Frequency/ timing	— Once before rainy season and once in dry season (i.e. every six months)	— Identify positive cases in health care facilities then do mass screening (200 people per positive case) at village level as routine activity in Thailand		
A.5.2. Staff/teams	— VMWs and special provincial teams to do	— Done regularly by provincial malaria team as part of routine active		

	screening and treatment	case investigation at village level		
A.5.3. Diagnostic tools	<ul style="list-style-type: none"> Microscopy and RDTs 	<ul style="list-style-type: none"> Priority to microscopy. then RDTs 		
A.5.4. Coverage	<ul style="list-style-type: none"> Aim for 100% coverage, but in reality (?): IEC prior to mass screenings needed, inform village heads Village-to-village screening (house-to-house?) demographic surveillance? GIS mapping 			
A.5.5. Provinces and districts for mass screening	<ul style="list-style-type: none"> Pailin, Somlat, Sampouv Loun; Veal Veng (?) 	<ul style="list-style-type: none"> Borai (Trat province), Pong Nam Ron and Soi Dao (Chanthaburi province) 		
A.6. Monotherapies and private sector practices	<ul style="list-style-type: none"> Recommendation to DDF to cancel registration of any artemisinin monotherapies 	<ul style="list-style-type: none"> Government ban on artemisinin monotherapies in private sector 		
A.7. Mass campaign approach to quickly scale up interventions to target population	<ul style="list-style-type: none"> Updating IEC/BCC materials including harmonized messages and campaigns with Thai counterparts 	<ul style="list-style-type: none"> Updating IEC/BCC materials including harmonized messages and campaigns with Cambodian counterparts 		

Round Table B. Vector control interventions and personal protection measures

B.1. General aspects and implications for VC

B.1.1 Defining vectors

- Known vector species: The main vectors in Cambodia are *An. dirus*, which is very anthrophilic, *An. minimus*, which is much less anthrophilic, and *An. maculatus*, which is mainly zoophilic. *An. dirus* is the main vector in stable forested areas in Pursat, whereas *An. minimus* predominated in changing environments on forest fringe and in areas of recent deforestation in Pailin. *An. barbirostris* has also recently been identified as a secondary vector.
- Vector incrimination: Elisa remains the primary method, but follow-up PCR of the positive specimens is needed for confirmation. Dissection with Elisa or PCR for species identification is an alternative.

B.1.2 Vector behaviour

- Resting behaviour

The study of indoor resting behaviour of vectors in Cambodia and Vietnam suggested very low ratios of indoor to outdoor resting for all vectors, particularly for *An. dirus* and *An. maculatus*. As demonstrated, *An. dirus* often rests briefly near the host before feeding.

- Biting cycle

From a study of hammock nets, it was found that a significant proportion of biting occurs before 10.00 pm. This was particularly the case for *An. Maculates*, for which 56% of bites occurred before 10.00 pm, compared to 38% for *An. dirus* and 28% for *An. minimus*.

- Endophagy

Biting indoors in open housing structures was generally much higher than in closed structures. This difference was particularly notable for *An. Minimus*, for which the biting rate per person per night was 7.9 in open housing structure versus 0.6-1.4 in closed structures. This compares with 1.3 versus 0.3-0.6 for *An. dirus*.

B.1.3. Parasite prevalence rates

A cross sectional survey conducted in Pailin and Pursat in 2005 showed that malaria prevalence ranges between 8% and 13%. Many are asymptomatic carriers. A majority of infections were due to *P. vivax* rather than *P. falciparum*.

B.1.4 Implications for vector control

Vector control is particularly challenging because the vectors are predominantly exophilic and exophagic and some biting take place in the early evening (up to 50% according to some studies). *An. dirus* is highly anthropophilic, *An. minimus* is moderately zoophilic and *An. maculatus* is very zoophilic in the presence of cattle.

B.2 Review of proposed vector control interventions

B.2.1 Insecticide-treated mosquito nets

For the main vectors, most (but not all) biting occurs after 10:00 pm and therefore bed nets can clearly be protective. Although the majority of people do sleep under nets, most of nets are not treated. Therefore, a priority for vector control is to achieve complete coverage of the population at risk with insecticide-treated nets, preferably LLINs.

The situation requires a combination of free distribution of ample numbers of LLINs, combined with simultaneous retreatment of the existing nets, using a wash-resistant long lasting insecticide which costs around US\$ 1.5 per tablet.

The product(s) selected should be approved by WHOPES, and should be a long-lasting net with a strong killing effect. Immediate procurement decisions should not be delayed, but whenever possible there should be specific investigation of consumer preferences, which should contribute to the procurement decision. Taking these preferences into account may help to increase the proportion of the target population who prefer our LLINs to the locally supplied nets they are already using.

Distribution systems based on local health systems are established in both Cambodia and Thailand. In Thailand, local distribution involves Village Health Volunteers, who look after ten households, and Malaria Volunteers in endemic areas who look after the village. In Cambodia, the systems and operating procedures exist, but need to be scaled up and consolidated to achieve new targets. Some form of salary for local health functionaries is likely to be necessary. Simply giving nets is not enough: thorough IEC/BCC campaigns on proper usage will also be needed. In particular, the attitude that nets are not needed in the forest because there are few mosquitoes there compared to the abundant *Culex* populations in the village needs to be addressed.

The commercial exchange value of new LLINs given away should be removed by taking them out of the packaging. All impregnated products (LLINs, hammocks/hammock nets) for distribution should be labeled clearly with their treatment status and date for the sake of traceability; a unique serial number may be sufficient for this if good records are kept.

The approach to monitoring and evaluation (M&E) should track delivery operations and employ surveys, aiming for 100% coverage in target districts with extra spare nets for forest workers. It should seek to investigate, analyze and overcome the reasons why coverage remains incomplete – including and especially areas, communities and social sub-groups that are underserved, for example because of social exclusion, migration and mobility.

The recommended strategy does not rely on private sector involvement, but it does acknowledge and take advantage of the fact that the private sector already makes a substantial and potentially valuable contribution to the existing high level of untreated net coverage, both in the village and in the forest.

There is scope for further development by converting the existing supply of ordinary untreated nets (and hammock-nets) into long-lasting/wash-resistant insecticidal nets, perhaps specifically focused on supplying to forest-markets, perhaps more broadly including the supply to the non-endemic areas from which migrant workers come.

B.2.2 Long-Lasting insecticide-treated hammocks and long-lasting insecticide-treated hammock-nets

Adult males going to the forest often sleep in hammocks, and people often sit in hammocks in the evening before going to sleep. Hammock-nets are commonly available, but even with insecticide can protect only a sleeping occupant, not someone sitting in the hammock. Insecticide-treated hammocks have been developed, with a flap to protect the user's legs when sitting. Compared to untreated control hammocks, the Olyset® hammock were found to increase protection against *An. minimus* by 44%, and to a lesser extent from *An. dirus* and *An. maculatus*. This suggests that the aim should be complete coverage of the forest worker population with insecticide-treated hammocks and nets.

The LLIN hammocks should be produced and made easily available for collection (for example in or near forest markets) for forest-goers to obtain. They should be made available free of charge bearing in mind that this will compete with the current commercial trade in ordinary untreated hammocks.

Treatment with long-lasting insecticide kit of existing untreated hammock-nets should be carried out during campaigns for treating the other existing untreated bed-nets.

B.2.3 Insecticide treated materials

In order to increase the possibility of personal protection, the development of appropriate insecticide treated materials such as blankets and clothing should be explored and the engagement of industry in this process should be encouraged. There may well be scope for imaginative use of insecticide treatment of the materials that people already take to the forest, or could easily take, and this should be investigated in participatory formative research with forest-going workers.

The treatment of the traditional all-purpose scarf (so-called locally "kroma") was discussed, but these (mostly cotton) scarves are normally washed at least once or twice a day, and no insecticide treatment is available that can withstand this level of washing.

B.2.4 Indoor residual spraying (IRS)

IRS is regarded in Thailand as an intervention with an excellent record of success. However, because the vectors are predominantly exophilic, the effect of IRS is likely to be incomplete and it is not likely to interrupt transmission in forest fringe areas. IRS may therefore be helpful, especially where the skills and infrastructure already exist, but it should not be regarded as a substitute to the priority of ensuring 100% LLIN coverage.

It may be helpful (because of the pre-prandial resting of some vectors) to spray the outdoor as well as the indoor walls, especially where people sit outside in the evening. Spraying the forest plots in addition to the villages is also important wherever these exist. It should be noted that IRS is logistically demanding and potentially expensive, especially in places where the infrastructure and local skills do not already exist and would need to be created.

Further research is needed on the relative importance as transmission sites of (a) villages; (b) forest farms and other places near but not inside the village; and (c) inside the forest itself.

Pyrethroids are currently used for IRS in Thailand and largely as pesticides for agriculture, but there are suggestions that pyrethroids should be reserved for use to (re)impregnate conventional nets, and should be avoided in IRS because spraying may select for resistance. According to this view, alternatives such as carbamates and organophosphates should be preferred, despite the shorter residual activity of some of these. Long acting DDT is now illegal in Thailand but not in Cambodia and should not be recommend for IRS as cross resistance occurs with pyrethroids.

B.2.5 Repellent

The role of repellents in personal protection was discussed as a means of bridging the gap in vector control. A recent study in South America shows promising results showing a significant decrease in the number of mosquito bites but data are otherwise limited. There is scope for investigation of the potential of personal repellents, especially those that are already or could easily be used by the population at risk. There are existing Diethyltoluamide (DEET)-based and citronella-based examples of repellents.

There are issues about formulation: in Thailand there is interest in the potential of marketing repellent in powder.

If such complementary interventions are to be employed they should be piloted first with adequate assessment of their quality and safety and accompanied by appropriate Communication for behavioural Change (BCC) to ensure proper use.

B.2.6 Larval control

An. dirus breed in small forest pools, *An. maculatus* in various pools in forests and open settings, while *An. barbirostris* breeds in a wide variety of scattered sites. Therefore, attempting to control breeding through larvicides and environmental control measures would be very difficult. The use of fish to decrease larval populations was discussed. In Thailand this approach is considered to have a useful role in control. Because of methodological design problems however, rigorous evaluation of the effectiveness of this method is virtually impossible, and decisive evidence either way is unlikely to be obtained.

B.2.7 Fogging

Although fogging has been used for dengue control in Thailand and could potentially be an effective means of dealing with exophilic vectors, it requires repeating at very short intervals (one week), and is therefore not very practical. There is very limited evidence from Central America that ULV applications in densely vegetated areas can leave an insecticidal film on the surface of the vegetation that has a brief residual activity against forest-loving vectors. This can never be a routine, sustained or frequently employed control measure, and is not appropriate with current levels of endemicity; however, it may later have a limited role at the end stage of an elimination campaign, when there may sometimes be an urgent need to suppress immediate transmission around the location where a recent case has been detected.

B.3 Monitoring and evaluation indicators in vector control

B.3.1 Coverage

Coverage (ownership and actual usage) of nets and hammocks and hammock-nets and their treatment status is important to be monitored. They can be measured through surveys using established methods; however, it

has to be noted that current methods are household-based and thus may miss mobile groups and visitors from non-endemic areas. New survey methods must be developed to track these vulnerable groups. GPS/GIS integrated systems will be helpful in the design of surveys, tracking of coverage (and gaps in coverage) and planning future modifications.

B.3.2 Epidemiological indicators

- All parasite-positive individuals, and all survey participants, should have their net usage and the treatment status of the net, together with other risk-related personal information, collected.
- In cross-sectional surveys, prevalence and serology should be related to VC intervention coverage. (Serology has many advantages as an indirect estimate of transmission intensity).

B.3.3 Entomological indicators

- Vector sampling: this should be done in villages and forest plots and, as far as possible, wherever people go. Human landing catches (with careful attention to adequate chemoprophylaxis or intermittent presumptive treatment and good follow-up) is likely to be indispensable; alternative trapping methods need to be validated. Density should be expressed as bites-per-person-night, by species and setting. Animal bait is a useful supplement.
- All specimens needed to be tested for sporozoites (see above). Continued investigation of vector behaviour (anthropophily and endophily) in sentinel sites should be carried out. Parasitic dissections are useful where possible and especially relevant to IRS.
- Insecticide susceptibility should be performed in sentinel sites.

B.3.4 Social studies

- Should concentrate on qualitative and quantitative investigation of attitudes to, and use of, all personal protection measures. Adaptation of novel personal protection such as repellents and hammocks/hammock-nets should be studied.

Round Table C. Mobile and migrant populations/Cross-border issues

C.1. Definitions and magnitude of migratory patterns

- Mobile population – a group of people moving, who stay in one place not more than six months, and could be both people within and outside country.
- Migrant population – a group of people who stay in one place for more than six months.
- Not much precise knowledge on actual numbers of mobile population and migrants is available. Where they came from and where they are going to – within countries and across borders from Cambodia to Thailand, in Thailand from west to east and in Cambodia from north to south.
- 1020 malaria cases of foreigners were recorded in 2007 in six provinces of Thailand bordering Cambodia.
- Mapping of the mobile/migrant groups, including information on seasonality, can be carried out by using community-based approaches using VHWs, VHV, local authorities (including at check points) and health-care facilities. This would give an estimate of the size of this population and number of migrants/mobile population actually using health services
- There are serious and changing over time politically driven regulations and policy concerns in Cambodia and Thailand for migrants (e.g. impacting on the availability to and use of health services by migrants)

C.2. Towards harmonization of cross-border malaria control activities

- There is a need to harmonize malaria control or pre-elimination strategies between Cambodia and Thailand, e.g. to ensure consistent health and malaria messages to mobile and migrant populations.
- Same drugs (ACTs)
- Same treatment regiment – 3 days
- Similar diagnosis criteria and methods

- Similar cross country IEC messages/materials in both languages (Khmer and Thai and possibly Burmese, since 25% of migrant workers in Trat province ,Thailand, are recorded from Myanmar)
- Similar key surveillance indicators supported by GPS/GIS communication technologies both sides

C.3. Surveillance mechanism models

- Regular sharing of information through bilingual cross-border meetings and use of same interconnected GPS/GIS-based technologies and database in both sites.
- Look at the MBDS system: district-to-district planning, monitoring and evaluation of interventions.
- Ensure capacity building on both sides in data management and cross-country reporting with focus on strengthening district capacity backed up by provinces

C.4. Boundary border surveillance

- Six official immigration check points are running between Cambodia and Thailand.
- Ensure same checking procedures and recording agreement on both sides (by using/building on existing mechanisms border police involvement? MoUs?).
- Screening procedures of people crossing border have to be considered and investigated.
- Cambodia: it is important to document and target internal migrants by training and equipping mobile health posts, developing a separate set of forms (or integrate info in existing ones?). This has still to be initiated.
- Need to advocate and explain to local authorities and policy-makers and private sector in Thailand.
- Concentrate on zones/provinces where malaria is still endemic.
- Strengthen analysis of current data to better identify high-risk groups.

- Mechanisms to involve communities in data collection and analysis need to be explored and strengthened in addition to the routine health information system (HIS).
- Cambodia is scaling up the community-based VHW strategy. More supportive staff at OD level (with data management skills) and in health posts will be posted and incentives provided to volunteers and community workers.
- Due to difficulty in accessing public health facilities, mobile people go to unregulated private providers. How to collect this important information and increase access to the public system are important questions.

C.5. Current models to consolidate information on internal and cross-border population

- Cambodia: there is a serious problem to routinely record the number of patients seeking care from private providers.
- Local authorities to be involved to facilitate exchange of info and dialogue with private providers.
- Cambodia: the passive detection system of malaria cases is weakened by low health-care coverage and performance.
- Thailand has good forms and systems for THAI and non-THAI people but there is a need to document practices of unrecorded migrants and mobile population.
- Cambodia: as an interim solution before reaching 100% PHC coverage, VHWs and VHV are recommended to be posted in all endemic villages.
- Cambodia is to develop a surveillance report system based on/articulated with THAI forms.

C.6. Current effort/initiatives addressing migrants' issues

- border control or perimeter control measures through multisectoral approaches including owners' involvement.
- Systematic parasitological investigation at checkpoints should be supported both sides.

Mobile and migrant populations: issues and suggestions to address them

Cambodia would focus on internal migration while Thailand would focus on cross border issues and access to health care by mobile population and migrants to reduce transmission risk in Thailand. But the two approaches will inter-link to ensure both internal and cross border migration is addressed.

Potential sites to be considered:

Thailand

Chantaburi
Trat
Sakeo
Srisaket
Surin

Cambodia

Pailin
Pursat, Kokong
Bathabong, Bantey Meachey
Pravihea
Odor Meachey

Issues	Looking at	Approach
1. Collection and effective use of strategic information on migration patterns	<ul style="list-style-type: none"> – Numbers – Demographic information – Pattern – Type/occupation – Malaria and basic health information 	<ul style="list-style-type: none"> – Mapping at community level (village volunteers, migrant volunteers), health facility and checkpoints at border – Information links across borders (by using modern technology integrating GPS/GIS and telephone capacities in one instrument) – Collecting and sharing info: <ul style="list-style-type: none"> • GPS/GIS/mobile phone, hand-written mapping, normal manual and electronic forms, surveys • Electronic commonly shared database in Thai and Khmer perhaps in Burmese language • Regular joint meetings at all levels • Set up and maintain a common restricted access website (password protected)
2. Establishing and harmonizing cross-border activities	<p>Critical review of current systems</p> <ul style="list-style-type: none"> – Surveillance – Active investigation 	<p>From review of current systems to piloting innovative approaches</p> <ul style="list-style-type: none"> – Surveillance <ul style="list-style-type: none"> • health service report • community report • border surveillance • MBDS approaches • Electronic data base/communication tools

Issues	Looking at	Approach
	<ul style="list-style-type: none">– Policy – Continuum (harmonization) of malaria prevention and control at both sites	<ul style="list-style-type: none">– Policy<ul style="list-style-type: none">• multisectoral approach: ministries of health, interior, defense, foreign affairs and labor; civil society and NGOs – Continuum of malaria prevention and control

Round-table discussion: cross-cutting issues on MDR containment elements: health systems, capacity building, private sector, village workers and volunteers (with focus on Cambodia)

Key issue 1: All effort must be made to ensure that the national malaria programme and partners in Myanmar are progressively engaged in containment measures aligned with the Thai and Cambodian programme

Key issue 2: Do we risk selecting for resistant strains?

Target group	Interventions	Methodology	Coverage	Timing	Responsible	Funding
	Stimulate AMFm to initiate operations in the Mekong region as a priority (to increase access to subsidized drugs by the private sector).	Initiate discussion with interested donors and GFATM		Immediate	WHO and partners	
D1 Private sector (overall)	Quantification of ACT and RDT requirements (both for replacement stock and annual consumption).	Rapid assessment of private sector wholesalers and drug-seller stocks of AMT. Estimate incidence-based on public sector and NGO sector PCD data and extrapolate for private sector. USP (Essential Drugs Bureau)/MORU data on illegal imports.	Representative selection of sites.	Immediate	CNM, DDF and PSI with NGO involvement.	Ministries, of health Sector Support Project (involve donors). AMFm. ADB?
	Subsidize ACT AND RDTs.	Following AMFm methodology. MoH to launch. Crucial to avoid any stock-outs and procure adequate supplies in good time.	Country-wide	Immediate	PSI then AMFm	
	Ban importation of AMT	Letter from CNM to MoH. DDF to take action to prevent further imports of AMT.	Central level	Immediate	CNM and MoH and DDF.	
	Inform private sector of changes in policy	Fliers, mass media, detailers (sales reps), professional associations (pharmacists, nurses and doctors) and community groups.	Country-wide but emphasis initially in target provinces.	Immediately following launch of subsidized ACT.	CNM and PSI.	
	Public information campaign: Importance of diagnosis and rational use of drugs; counterfeit drugs.	Mass media (radio, and TV); provincial intersectoral committee meetings (other ministries, NGOs, provincial governors, schools etc), IEC/BCC materials, community programmes, village meetings. Integrated/interprogramme efforts where possible (e.g. deworming).	Country-wide, but emphasis initially in target provinces.	Immediately following launch of subsidized ACT.	CNM, PSI, FHI, PFD, HU, SCF and others in coordination with MEDICAM (health NGO umbrella org).	

Target group	Interventions	Methodology	Coverage	Timing	Responsible	Funding
	Replace existing stocks of AMT with ACT(s).	Starting at wholesalers' level and working out to periphery: exchange/buy and destroy AMTs. Amnesty of three months after which AMTs will be confiscated and fine imposed. Introduce loyalty schemes.	Country-wide but emphasis initially in target provinces.	Immediately following launch of subsidized ACT.	PSI and DDF.	
	QA/implementation research.	Baseline and follow-up surveys assessing consumers' understanding of key messages.	Sentinel sites	Before, during and after intervention.	CNM/PSI	
D2 Private sector (regulated)	Increased knowledge and capacity in EDAT.	Education and training: Formal training through PSI's "medical retailers" (present capacity 1000 outlets per year) - intensive information campaign, rely on existing mechanisms [local associations, Rotary, etc.]. Work with sales representatives for trickle down training. Link with universities and colleges for longer-term impact.	Country-wide but emphasis initially in target provinces.	Immediately following launch of subsidized ACT.		
D3 Private sector (unregulated)	Increased knowledge and capacity on EDAT.	Trickle-down training from regulated private sector. Formal training through PSI's "medical retailers". Approach Bhuddist monasteries to help delivering messages influencing drug sellers. Use existing social events to raise awareness.	Country-wide but emphasis initially in target provinces.	Immediately following launch of subsidized ACT.	CNM, local authorities, NGOs	
	Increase knowledge overall.	Thai model: Free college training without the need for an entrance exam to encourage those engaged in good practices.	Innovative encouraging systems to be designed	Long term.	CNM, MOH	
D4 VHV's (VHSG)	Upgrade to VMW (mobile where appropriate).	Using existing training methodology. To select 1 mixed gender team (2 people) per 500 inhabitants. Incorporate smear-taking for cross-checking RDT-negative cases.	All static communities within 0.2 km of forest (237000 population) or up to 1 km (510000 population).	Immediately	CNM and partner NGOs.	
D5 VMWs	Expansion	Using existing methodology and tapping existing human resources where possible... 1 mixed gender team per 500 population. Incorporate smear-taking for RDT-negative cases.	All static communities within 0.2 km of forest (237000 population) or up to 1 km (510000 population).	Immediate	CNM and partner NGOs.	
	Review	Assess endemicity based on PCD (RDT and blood	As above	After one year	CNM and partner	

Target group	Interventions	Methodology	Coverage	Timing	Responsible	Funding
		smears) and decide on whether to suspend malaria diagnosis and treatment where appropriate.			NGOs.	
	Strengthen performance of VMWs.	Provide realistic and consistent financial and other incentives (such as free health-care for families). Ensure regular supervision and feedback.	Country-wide	Immediately.	CNM and partner NGOs.	
D6 Public sector (static)	Strengthen microscopy network.	60 microscopes already planned under GFR6 (30 in 2008 and 30 in 2011). Better involvement of private sector and NGOs where appropriate.	Target provinces.	Immediately.	CNM and partner NGOs.	
	Further strengthen capacity of health workers.	Continued integrated training and supportive supervision. Ensure carrier development.	Countrywide.	Ongoing.	CNM and other MoH departments.	
D7 Thai-Cambodia cooperation.	Bilateral meetings already planned under GFR6 (included in the bilateral committee agenda).	Meetings, accords, district - to-district planning and monitoring of operations.	two countries	Ongoing.	WHO, CNM, BVBD and partners	

Annex 3

List of participants

Ministries of Health, National Malaria Control Programmes

Cambodia

H.E. Dr Duong Socheat

Director

National Centre for Parasitology
Entomology and Malaria Control

Ministry of Health

372 Monivong Blvd, Phnom Penh
Cambodia

Tel: +855 12 815 950

Fax: +855 23 996 202

E-mail: socheatd@cnm.gov.kh

Dr Khunbunnarann Ly

CDC

Ministry of Health

Cambodia

Tel: +855 23 880 532

Fax: +855 23 880 532

E-mail: narannlee@gmial.com

Dr Kheng Sim

Vice Director, National Centre for Parasitology
Entomology and Malaria Control

No. 372, Monivong Bldg, Corner Street 322
Phnom Penh

Cambodia

Tel: +855 23 996 202

Fax: +855 23 996 202

E-mail: khengsim@cnm.gov.kh

Dr Sochantha Tho

Chief of Technical Office

#372 Monivong Bldg.

P.O. Box 1062, Phnom Penh

Cambodia

Tel: +855 23 996 202

Fax: +855 23 996 202

E-mail: sochanthat@cnm.gov.kh

Dr Yi Povaruth

Senior Staff Technical Bureau

National Centre for Parasitology

Entomology and Malaria Control Programme

Ministry of Health

#372 Monivong Blvd.

P.O. Box 1062, Phnom Penh

Cambodia

Tel: +855 23 99 62 02

Fax: +855 23 99 62 02

E-mail: yiporavuth@yahoo.com

Dr Leang Rithea

Head of CNM Research Unit

National Centre for Parasitology, Entomology
and Malaria Control Programme

Ministry of Health

#372 Monivong Blvd.

P.O. Box 1062, Phnom Penh

Cambodia

Tel: +855-23 99 62 02

Fax: +855-23 99 62 02

E-mail: leangrithea@cnm.gov.kh

Dr Chroeng Sokhan

Vice Director, Department of Drugs and Food

Ministry of Health

#372 Monivong Blvd.

P.O. Box 1062, Phnom Penh

Cambodia

Tel: +855 23 88 0969

Fax: +855 23 88 0696

E-mail: sokhan_c@online.com.kh

China

Dr Gang Xia

Ministry of Health, Beijing

China

Tel: +86 10 6879 2361

Fax: +86 10 6879 2514

E-mail: xiagang@moh.gov.cn

Thailand

Dr Wichai Satimai

Director, Bureau of Vector Borne Diseases

Department of Disease Control

Ministry of Public Health

Tiwanond Road, Nonthaburi 11000

Thailand

Tel: +66 2 590 3121

Fax: +66 2 591 8422

E-mail: wichaisatimai@yahoo.co.th

Ms Saowanit Vijaykadga
Technical Officer, Malaria Cluster,
Bureau of Vector Borne Diseases
Department of Disease Control
Ministry of Public Health
Tiwanond Road, Nonthaburi 11000
Thailand
Tel: +66 2 590 3126
Fax: +66 2 591 8422
E-mail: saowanit@health.moph.go.th

Mr Dakorn Limrat
Vector Control Specialist,
Bureau of Vector Borne Diseases
Department of Disease Control
Ministry of Public Health
Tiwanond Road, Nonthaburi 11000
Thailand
Tel: +66 2 590 3124
Fax: +66 2 591 8422

Mr Suchart Patipong
Chief of Vector Control,
Bureau of Vector Borne Diseases
Department of Disease Control
Ministry of Public Health
Tiwanond Road, Nonthaburi 11000
Thailand

Dr Pongwit Bualombai
Chief of Reference Laboratory,
Bureau of Vector Borne Diseases
Department of Disease Control
Ministry of Public Health
Tiwanond Road, Nonthaburi 11000
Thailand
Tel: +66 2 590 3128-9
Fax: +66 2 591 8422
E-mail: pongwitb@yahoo.com

Mrs Bussabong Chaothanont
Social Science,
Bureau of Vector Borne Diseases
Department of Disease Control
Ministry of Public Health
Nonthaburi 11000
Thailand
Tel: +66 2 590 3151
Fax: +66 2 591 8427
E-mail: busabong@health.moph.go.th

Mrs Pornpimon Ghamtao
Epidemiologist, Bureau of Vector Borne
Diseases
Department of Disease Control
Ministry of Public Health
Tiwanond Road,
Nonthaburi 11000
Thailand

Dr Supawadee Konchum
Epidemiologist, M&E,
Bureau of Vector Borne Diseases
Department of Disease Control
Ministry of Public Health
Tiwanond Road, Nonthaburi 11000
Thailand
Tel: +66 2 590 3134
Fax: +66 2 591 8422
E-mail: jiabk@yahoo.com

Mrs Kesanee Kladphaung
Social Science, Bureau of Vector Borne
Diseases
Department of Disease Control
Ministry of Public Health
Tiwanond Road, Nonthaburi 11000
Thailand
Tel: +662 590 3127
Fax: +662 591 8422
E-mail: keskla@health.moph.go.th

Viet Nam

Ms Ta Thi Tinh
Head of Malaria Treatment and Research
NIMPE, Hanoi
Viet Nam
Tel: +84 4 854 2349
Email: tinhtt@nimpe.vn

Representatives of national and Regional Institutions

Dr Pratap Singhasivanon
Secretary General/Coordinator and Dean
Faculty of Tropical Medicine,
Mahidol University,
SEAMEO TROPMED Network
420/6 Ratchawithi Road, Bangkok 10400
Thailand
Tel: +66 2 354 9100 ext. 1321
Fax: +66 2 354 9198
E-mail: tmpsh@mahidol.ac.th

Prof Polrat Wilairatana
Coordinator, WHO Collaborating Centre for
Clinical Management of Malaria
Faculty of Tropical Medicine,
Mahidol University
420/6 Ratchawithi Road, Bangkok 10400
Thailand
Tel: +66 2 354 9100 ext. 1454
Fax: +66 2 354 9168
E-mail: tmpwl@mahidol.ac.th

Associate Prof Srivicha Krudsood
Malaria Clinical Research, Faculty of Tropical
Medicine
Mahidol University
420/6 Ratchawithi Road, Bangkok 10400
Thailand
Tel: +66 2 354 9159
Fax: +66 2 354 9158
E-mail: tmsks@mahidol.ac.th

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

Technical Assistance/Consultants

Dr Maria Dorina Bustos
Medical Specialist III
Research Institute for Tropical Medicine
Department of Health
FICC, Alabang, Muntinlupa City
Metro Manila,
Philippines
Tel: +632 807 2636-7 loc 227 or
+632 809 7599
Fax: +632 842 2828, +632 842 2245
E-mail: dorinabustos@yahoo.com

Prof Marc Coosemans
Unit of Vector Control, Dept of Parasitology,
University of Antwerp,
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

Dr Sean Hewitt
VBDC Consulting, UK
Gilfach Uchaf, Saron, Llandysul,
Carmarthenshire SA44 5EJ
United Kingdom
Tel: +44 (0) 1559 371 127
Fax: +44 (0) 7870 608 255
E-mail: sean.hewitt@vbdc-consulting.com

Dr Jonathan Lines
London School of Tropical Medicine
and Hygiene (LSHTH)
United Kingdom
Tel: +44 207 927 2674
E-mail: Jo.Lines@lshtm.ac.uk

Dr Giuseppina Ortu
London School of Tropical Medicine
and Hygiene (LSHTH)
United Kingdom
Tel: +44 776 511 8494
E-mail: giuseppina_ortu@yahoo.it

Dr Sylvia Meek
Technical Director,
Malaria Consortium Development House,
56-64 Leonard Street,
London EC2A 4LT
United Kingdom
Tel: +44 207 549 0210
Fax: +44 207 549 0211
E-mail: s.meek@malariaconsortium.org

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

Dr Shunmay Yeung
Oxford-Mahidol Collaboration, Thailand
24 Corsica Street
London N5 1JY
United Kingdom

Prof Nicholas J. White
Oxford 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

Donors

Dr Tom Kanyok
Bill and Melinda Gates Foundation
Box 23350, Seattle, WA 98102
USA
Email: thomas.kanyok@gatesfoundation.org

Dr Thomas G. Brewer
Senior Program Officer,
Infectious Diseases Development
Global Health Program

Bill and Melinda Gates Foundation
Box 23350
Seattle, WA 98102
USA
Tel: +206 709 3314
Fax: +206 709 3170
E-mail: thomas.brewer@gatesfoundation.org

Dr Gretchen Margaret Meller
Associate Program Officer,
Infectious Diseases Global Health Program
Bill and Melinda Gates Foundation
PO Box 23350
Seattle, WA 98102
USA
Tel: +206 770 1718
E-mail: gretchen.meller@gatesfoundation.org

Dr John MacArthur
USAID/Regional Development Mission - Asia
GPG Witthayu Tower, Tower A,
93/1 Wireless Road,
Bangkok, 10330
Thailand
Tel: +66 2 263 7411
Fax: +66 2 263 7499
Email: jmacarthur@usaid.gov

Mr Toshiki Ono
First Secretary, Embassy of Japan in Thailand
177 Wireless Road, Lumpini,
Pathumwan, Bangkok 10330
Thailand
Tel: +66 2 696 3000 ext. 509
Fax: +66 2 207 8517
Email: toshiki.ono@mofa.go.jp

Partners

Dr Celine Costello Daly
Family Health International,
Asia/Pacific Regional Office
2nd Floor, Sindhorn Building, Tower 1
130-132 Wireless Road, Lumpini
Phatumwan, Bangkok 10330
Thailand

Dr Mark Fukuda
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: +62 2 644 4784
E-mail: mark.fukuda@afirms.org

Dr Philippe Guyant
Malaria Programme Manager
26, St 334, Boeung Keng kang 1
Khan Chamcamnorn PO Box 551,
Phnom Penh
Cambodia
E-mail: ph.guyant.pfd@online.com.kh

Dr Alden Henderson
Epidemiologist
Ministry of Public Health
Tiwanond Road, Nonthaburi 11000
Thailand
E-mail: ahenderson@th.cdc.gov

Dr Jim Hopkins
Program Manager, Public Health Programme
Kenan Institute Asia,
Siripanich Building, 4th Floor,
191 Huay Kaew Road, Muang District
Chiang Mai 50200
Thailand
Tel: +66 53 213 039
Fax: +66 53 213 039
E-mail: jimh@kiasia.org

Ms Diane Freeman
Program Manager
Population Services International (PSI)
Cambodia
Tel: +855 12 222 380
E-mail: dfreeman@psi.org.kh

Mr Chris Jones
Country Representative
Population Services International (PSI)
Cambodia
Tel: +855 012 222 380
E-mail: cjones@psi.org.kh

Dr Nigoon Jitthai
Migrant Health Programme Manager
International Organization for Migration (IOM)
Thailand
Tel: +66 2 343 9341
Fax: +66 2 343 9399
Email: njitthai@iom.int

Prof Harald Noedl
Institute of Specific Prophylaxis and
Tropical Medicine,
Medical University of Vienna
Kinderspitalgasse 15
A-1090 Vienna
Austria
Tel: +43 1 4277 64882
Fax: +43 1 4277 64899
E-mail: harald.noedl@meduniwien.ac.at

Dr Christopher Plowe
Doris Duke Distinguished Clinical Scientist
Center for Vaccine Development
University of Maryland, School of Medicine
685 West Baltimore Street
HSF1-480 Baltimore MD 21201, USA
Tel: +1 410 706 2491
Fax: +1 410 706 1204
E-mail: cplowe@medicine.umaryland.edu

Dr Frederic Arieu
Molecular Epidemiology Unit
Pasteur Institute in Cambodia
5 Boulevard Monivong
Phnom Penh, Cambodia
E-mail: fariey@pasteur-kh.org

Mr Ruangdech Pongprom
Food Security Data Analyst,
The United Nations World Food Programme
Bureau for Asia, Bangkok, Thailand

Mr Axel Pustan
Regional VAM, Spatial Data Analyst
The United Nations World Food Programme
7th Floor, Wave Place Building
55 Wireless Road, Pathumwan
Bangkok, Thailand
Tel: +66 2 655 4115
Fax: +66 2 655 4415
E-mail: Axel.Pustan@wfp.org

Mrs Janet Robinson
Director of Research,
The Family Health International
Asia/Pacific Regional Office
2nd Floor, Sindhorn Building, Tower 1
130-132 Wireless Road, Lumpini
Phatumwan, Bangkok 10330
Thailand
Tel: +66 2 263 2300
Fax: +66 2 263 2131
E-mail: jrobinson@fhibkk.org

Mr Michael Sheinkman
Senior Regional Programme Advisor
Vulnerability, Analysis and Mapping (VAM)
World Food Programme, Bureau for Asia
Wave Place Bldg, 7th Floor,
55 Wireless Road, Lumpini, Pathumwan,
Bangkok 10330, Thailand
Tel: +66 2 655 4115 ext. 2430
Fax: +66 2 659 4415
VSAT: 1353-2430
E-mail: Michael.Sheinkman@wfp.org

Dr George Watt
Epidemiologist & Tropical Medicine Consultant
The Centers of Disease Control and Prevention
The Ministry of Public Health
IEIP, DDC 7 Building, 3rd Floor, MOPH Soi 4
Nonthaburi 11000, Thailand
Tel: +66 2 591 1294
Fax: +66 2 580 0911
E-mail: GeorgeW@th.cdc.gov

Mr. Christopher Raymond
Regional Project Coordinator for
Southeast Asia
United States Pharmacopeia Drug Quality
and Information Program
Kenan Institute Asia,
Queen Sirikit National Conventional Center
2nd Floor, Zone D, Room 201/2
60 New Ratchadapisek Road, Klongtoey
Bangkok 10110, Thailand
Tel: +66 2 229 3131-2 ext. 222
Fax: +66 2 229 3130
E-mail: chrisr@kiasia.org

Ms Phungpit Kaewphet
Deputy Manager, Public Health Program
Kenan Institute Asia, Thailand
Tel: +66 53 213 039
Fax: +66 53 21 3039
E-mail: phungpit@kiasia.org

Ms Patchara Wongsuwan
Pharmaceutical System Research and
Intelligence Center, Thailand

Mr Herve d' Oriano
Regional Counselor for Health
The Embassy of France in Thailand
Regional Delegation
29 South Sathorn Road
Bangkok 10120, Thailand
Tel: +66 2 627 2141
Fax: +66 2 627 2111
E-mail: herve.doriano@diplomatie.gouv.fr

Observers

Dr Tim Wells
Chief Scientific Officer
Medicines for Malaria Venture
International Center Cointrin
Route de Pré-Bois 20
CH-1215 GENEVA 15
Switzerland
Tel: +41 22 7994067 (assistant ext. 4085)
Email: wellst@mmv.org

Secretariat

WHO Global Malaria Programme / Headquarters

Dr Kamini Mendis
Coordinator, WHO Headquarters
Global Malaria Programme
Avenue Appia 20, 1211 Geneva 27
Switzerland
Tel: +41 22 791 2766
Fax: +41 22 791 4824
E-mail: mendisk@who.int

Dr Pascal Ringwald
Antimalarial drug resistance
Global Malaria Programme
WHO Headquarters, Geneva
20 Av. Appia, 1211 Geneva 27
Switzerland
Tel: +41 22 791 34 69
Fax: +41 22 791 48 24
E-mail: ringwaldp@who.int

WHO-SEAR

Dr Charles Delacollette
Coordinator,
WHO-Mekong Malaria Programme
c/o Faculty of Tropical Medicine,
Mahidol University
420/6, 7th Floor, New Charlermprakiat
Building
Ratchawithi Road, 10400 Bangkok, Thailand
Tel: +66 2 643 5860
Fax: +66 2 643 5870
Email: delacollette@searo.who.int

Dr Maureen Birmingham
WHO Representative
Thailand
c/o Office of the Permanent Secretary,
Building 3, 4th Floor
Ministry of Public Health, Tiwanon Road,
Nonthaburi 11000, Thailand
Tel: +66 2 591 1514
Fax: +66 2 591 8199
Email: Birmingham@searo.who.int

Mr Chawalit Tantinimitkul
WHO Thailand
c/o Office of the Permanent Secretary,
Building 3, 4th Floor
Ministry of Public Health, Tiwanon Road
Nonthaburi 11000, Thailand
Tel: +66 2 590 1506
Fax: +66 2 591 8199
Email: chawalit@searo.who.int

WHO-WPR

Dr John Patrick Ehrenberg
Regional Advisor Malaria, Other Vector-borne
and Parasitic Diseases
WHO Regional Office for the Western Pacific
(WPRO)
Tel: + 63 2 528 9725
Fax: + 63 2 521 1036
E-mail: ehrenbergj@wpro.who.int

Dr Eva Maria Christophel
Medical Officer,
WHO Regional Office for the Western Pacific
(WPRO)
MVP, Manila
Philippines
Tel: +63 2 528 9723
Fax: +63 2 521 1036
E-mail: christophele@wpro.who.int

Dr Chang Moh Seng
Vector Control Specialist
WHO Cambodia
PO Box 1217, Phnom Penh, Cambodia
Tel: +855 2321 6610
Fax: +855 2321 6211
E-mail: changm@wpro.who.int

Dr Abdur Rashid
Medical Officer
Malaria, Other Vector Borne and
Parasitic Diseases
WHO Cambodia
PO Box 1217, Phnom Penh, Cambodia
Tel: +855 2321 6610
Fax: +855 2321 6211
E-mail: rashidm@wpro.who.int

Dr Deyer Gopinah
Medical Officer, WHO Lao PDR
Lao PDR
Tel: 856 21 413 431
E-mail: gopinahd@wpro.who.int

Mr Pricha Petlueng
Community Development / Communication
Specialist
WHO Lao PDR
Lao PDR
Tel: +856 21 413 431
Fax: +856 21 413 432
E-mail: petluengp@lwpro.who.int

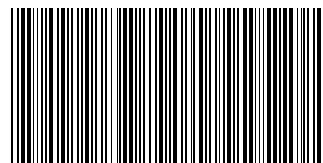
Recent studies have revealed the border area between Cambodia and Thailand to be the epicentre of emerging resistance of *Plasmodium falciparum* to artemisinins. Common cross-border strategies are, therefore urgently needed to address this global threat. At an informal consultation held in Bangkok, Thailand, in February 2008, national and international experts elaborated the main technical elements of a cross-border multi-sectoral containment strategy. The strategy is expected to improve the situation in the coming years by preventing the artemisinin-tolerant parasites from growing further, both in the Mekong region and outside. The report of this consultation consolidates the technical views of experts. However, the proposed technical approaches have not yet been validated. This has triggered the urgent need of operational research that is required to formulate appropriate strategies and interventions. Recommendations of this consultation were considered as the basis to finalize the proposal on cross-border strategy to contain the tolerant parasites, for submission to governments, partners and donors for short - and long-term funding.



**World Health
Organization**

Regional Office for South-East Asia

World Health House
Indraprastha Estate,
Mahatma Gandhi Marg,
New Delhi-110002, India



SEA-MAL-257