GLOBAL MALARIA CONTROL AND ELIMINATION:

report of a meeting on containment of artemisinin tolerance

19 January, 2008
Geneva, Switzerland

World Health Organization

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EXECUTIVE SUMMARY

Since 2003, evidence has been accumulating that artemisinin-based combination therapies (ACTs) are less effective against *Plasmodium falciparum* on the Thai–Cambodian border. If this is due to the emergence of parasites that are resistant to artemisinin derivatives, the global effort to control and eliminate malaria is under threat. To respond to this global emergency, the World Health Organization (WHO) has taken steps for confirmation and containment. The meeting reported here was convened at short notice, as an extension of a larger technical meeting, to take the opportunity to obtain expert advice on the optimal technical strategies for the prevention or containment of malaria on the Thai–Cambodian border.

Interim data were presented from Pailin, western Cambodia, which confirm that parasites that are 'tolerant' to artemisinins have emerged, which exhibit uniformly prolonged clearance times after treatment with either artesunate plus mefloquine for 3 days or artesunate for 7 days and decreased efficacy of the latter regimen. Whether or not these parasites are labelled 'artemisinin resistant', urgent action must be taken to limit their spread.

The discussion focused on interventions to be made this year in three main areas: choice of antimalarial medicine, choice of vector control measures and details of a proposed campaign for mass screening and treatment. A comprehensive presentation was made on the operational issues, and there was a broad-ranging discussion on issues including the importance of the migrant population, the urgent need for surveillance data, management of *P. vivax* infection, the roles of different diagnostics and novel interventions.

In both Thailand and Cambodia, the currently recommended first-line treatment for *P. falciparum* malaria is artesunate plus mefloquine for 3 days. In Cambodia, however, use of artemisinin monotherapy is rife. If effective treatment could be given widely in combination with vector control measures, it is possible that resistant strains of *P. falciparum* could be eliminated. Although artesunate plus mefloquine for 3 days was still effective in Pailin, the results in other areas were poorer, and an alternative effective, well-tolerated drug was preferred. The objective of changing from the current recommendation to a co-formulated antimalarial drug combination is to limit the taking of artemisinin monotherapy by misuse of the co-blistered formulation. Use of the only potentially effective non-artemisinin-containing drug, atovaquone–proguanil, was discussed; however, dihydroartemisinin–piperaquine emerged as the most suitable, practical choice on the basis of

various technical and operational considerations. Use of this medicine will be subject to assessment of the quality and stability of the products available. The other option, atovaquone–proguanil, might also be useful, in addition to dihydroartemisinin–piperaquine. The choice of the medicine will be reviewed when other alternatives become available.

Vector control plays a crucial role in reducing the transmission of all malaria, including potentially drug-resistant clones. Knowledge of the behaviour of the vector and the human targets is therefore critical in choosing the most effective measures. The main recommendations were to cover rapidly all age groups in the target area with insecticide-treated nets, ideally long-lasting ones, plus insecticide-treated hammock nets and hammocks for protection for people staying overnight in the forest. In addition, research and development is needed on repellents and new materials, such as long-lasting insecticide-treated blankets.

A proposal for a campaign based on mass screening and treatment was presented. The objective would be to eliminate falciparum malaria from Pailin and the contiguous districts of Sampouv Loun and Samlot through detection of asymptomatic parasite carriers and rapid reduction of the parasite pool, starting at the end of 2008 or early 2009, during the low transmission season. The campaign would be undertaken by large teams, trained to perform rapid diagnostic tests and to treat patients with directly observed therapy. Two consecutive campaigns would be carried out. A system would be set up for passive and active case detection, including in migrant populations.

Issues identified as requiring further discussion and clarification included:

- Consideration of the use of microscopy with or without polymerase chain reaction (PCR) to identify malaria carriers with parasite densities below the limit of detection of rapid diagnostic tests;
- Systematic treatment with chloroquine for all symptomatic patients with a negative diagnosis of falciparum malaria; and
- Consideration of conducting the campaign in both the low and the high transmission seasons.

1. BACKGROUND

The border area between Cambodia and Thailand has been the epicentre of emerging malaria drug resistance since the 1970s, starting with resistance of *P. falciparum* to chloroquine, followed by resistance to sulfadoxine–pyrimethamine and then to mefloquine. Now, there is evidence that the parasite's sensitivity to ACTs has decreased in this area, implying that the parasite may be developing resistance to artemisinins, which form the basis of the most effective recommended treatment for falciparum malaria. If artemisinin resistance is confirmed, the threat to malaria control in the region and even globally would be enormous.

Recognizing the gravity of this global emergency, WHO has begun to take steps to (1) investigate if there is indeed artemisinin resistance, (2) define optimal strategies and prepare a plan to prevent or contain artemisinin resistance in the locality by interrupting and containing the transmission of malaria and (3) define a research agenda to support these actions.

This meeting was convened as an extension of a larger technical meeting on global malaria elimination. The objective was to define the optimal technical strategies for arresting and reversing the impending threat of resistance to artemisinins, as follows:

- Define the optimal technical strategies for containment of malaria transmission in the Thai–Cambodian border region.
- Define the content and outline of an operational plan to contain malaria transmission in the Thai–Cambodian border region.
- Define and set priorities for a research agenda based on critical gaps in knowledge.

2. IS THERE ARTEMISININ RESISTANCE?

2.1 CLINICAL TRIAL

Background and brief methods

The ongoing studies in Pailin are a collaborative effort, involving the Cambodian National Malaria Control Programme, the Institut Pasteur Cambodia, the Armed Forces Research Institute of Medical Sciences, Family Health International and the Faculty of Tropical Medicine, Mahidol University. A clinical trial in 2007 involved 40 patients with uncomplicated *P. falciparum* malaria (parasite density, > 10 000/µl). Patients were randomized to artesunate at 2 mg/kg per day for 7 days or artesunate at 4 mg/kg per day for 3 days and mefloquine at 15 and 10 mg/kg per day on days 3 and 4 (mefloquine plus artesunate for 3 days). They were followed up for 63 days.

Results

Follow-up of the final patients is still under way; however, the interim results show that there have been seven recurrences of falciparum infection, all in patients given artesunate for 7 days, with a median time to recurrence of 28 days (mean, 35 days). The results of the molecular analyses and drug levels are awaited. Ten patients also had recurrences with vivax malaria, five in each arm, all of which occurred on day 35 or later. Parasite clearance times were prolonged in all patients in both arms, the median time to a 50% reduction in parasites being 11 h with artesunate for 7 days and 9 h with mefloquine and artesunate for 3 days. The median times to 90% reduction were 27 h and 25 h, respectively. The median parasite clearance times were 87 h (42–120 h) and 78 h (36–114 h), respectively. In vitro susceptibility tests suggest that the parasites were not particularly resistant, except in one case.

Interim interpretation

The most likely explanation is the emergence or the selection of parasites with reduced ring-stage susceptibility, which would render them 'tolerant' to artemisinin derivatives. Whether this is labelled artemisinin 'resistance' will be decided after further research.

Other possible explanations for the results include inadequate absorption or unusual host metabolism of artesunate, parasites with unusual 'metabolism' or the ability to become dormant, splenic hypofunction or red blood cell abnormalities.

Next steps for confirmation and characterization

- Await the results of laboratory tests, including detailed pharmacokinetics profiles, in vitro susceptibility (ELISA, isotopic, schizont maturation, modified test to examine rings), molecular typing and analysis of known molecular markers of drug resistance.
- Conduct further studies in four sites: Pailin (Cambodia), Tasanh (Cambodia), Mae Sot (Thailand) and Bandarban (Bangladesh), as part of a WHO collaborative project funded by the Bill and Melinda Gates Foundation.
- Conduct clinical studies of the efficacy of artemisinin in China and Viet Nam, coordinated by the WHO Mekong Malaria Programme, with funding from the United States Agency for International Development.

2.2 DISCUSSION POINTS

Is the phenomenon artemisinin resistance?

Whether the observed phenomenon is labelled artemisinin 'resistance' or 'tolerance', it is clear that parasites in some parts of the region have had reduced sensitivity to ACTs for several years. The interim results of the Pailin study confirm uniformly prolonged parasite clearance times. Despite the relatively small size of the study, the uncorrected failure rate of 7 out of 20 in the arm receiving artesunate for 7 days is of great concern.

How far has the phenomenon spread?

In order to target the correct area for containment, the geographical extent of spread must urgently be defined, in particular in China and Viet Nam, where artemisinin derivatives have a long history of use. There is evidence of decreasing in vitro susceptibility in Yunnan (Yang et al., 2003), and the studies funded by the United States Agency for International Development should provide more data this year. The studies funded by the Bill and Melinda Gates Foundation will help to define the western boundary of the spread. There is real concern that, if the resistant clones are carried into Myanmar, the chances of successful containment will be diminished due to the extremely poor infrastructure in that country. Data from the Shoklo Malaria Research Unit suggest that since 2000 parasite clearance times have increased and there has been a small but significant decline in the parasitological efficacy of mefloquine plus artesunate for 3 days. A higher proportion of isolates have increased *pfmdr1* copy numbers, and there has been a significant change in susceptibility to mefloquine and artesunate in vitro.

Can artemisinin resistance be overcome by increasing the dose?

No difference was found between the 2 mg/kg per day and 4 mg/kg per day doses in the Pailin trial. This might mean that the dose was not high enough. In the next clinical trial in Pailin, therefore, doses of 6–8 mg/kg per day will be used. It may be, however, that the mechanism of action is such that sensitivity cannot be increased by increasing the dose.

Is the combination of artesunate plus mefloquine still effective?

The interim results presented suggest that there were no clinical failures among patients given mefloquine plus artesunate for 3 days. The sample size was, however, small (n = 20), limiting confidence in this result. Results from routine in vivo efficacy tests conducted in 2007 showed that the PCR-corrected failure rate with mefloquine plus artesunate for 3 days is almost 10% in Veal Veng. The main genetic factor that is correlated with mefloquine resistance is amplification of the *pfmdr1* gene, but most of the cases in Pailin had only one copy number. This presumably explained the good responses to mefloquine plus artesunate.

Why has artemisinin resistance emerged?

The Thai–Cambodian border has been the epicentre of the development of antimalarial drug resistance: evidence suggests that resistance to both chloroquine and sulfadoxine–pyrimethamine emerged in this area. The addition of chloroquine and then the addition of pyrimethamine to salt in Pailin in the late 1950s would have exerted an enormous selection pressure on the parasites, which is likely to have contributed to resistance. In addition, there is evidence that the South-East Asian parasites readily develop resistance to all antimalarial drugs (Rathod, McErlean, Lee, 1997).

Other behavioural and drug factors that might contribute to the emergence and spread of drug resistance, which are important to consider in planning for containment, are:

- Mobile populations and migrants: Historically, this has long been an area of population movement, with people travelling from within Cambodia and as far away as Myanmar, mainly to mine for gems or collect forest products. The population is a heterogeneous group, of whom little is known in terms of size, location and behaviour. Understanding and mapping their behaviour is essential for controlling drug-resistant malaria.
- Artemisinin monotherapy: Although the officially recommended treatment in both Thailand and Cambodia is mefloquine plus artesunate for 3 days, artemisinin monotherapy has been widely used in Cambodia, for a number of reasons. Most (70–80%) people with fever seek treatment

from the unregulated private sector, where artemisinin monotherapies are widely available and used. Artemisinins are popular because they are perceived to be effective, free from side-effects and relatively cheap. Although blister-packaged artesunate and mefloquine is provided free in the public sector, it is not popular because of the side-effects associated with mefloquine, and there are stock-outs. There are anecdotal reports that people split the blister packages and take only the artesunate. Use of sachets containing a mix of tablets, including antimalarials, is popular.

- Subtherapeutic levels of artemisinins: Subtherapeutic levels of artemisinins contribute to selection pressure and continued infectiousness. This may have resulted from under-dosing in recommended regimens or poor adherence by patients. In 2007, the mefloquine plus artesunate regimen was optimized in Cambodia, and in Thailand the duration of its recommended use was increased from 2 to 3 days. Concern remains, however, about adherence to the regimen.
- Substandard and counterfeit drugs: The widespread availability of counterfeit artesunate is well documented (Newton et al., 2008). These sophisticated products often contain no or very little artesunate. In addition to the obvious potential dangerous consequences for patients, their use may also contribute to continued infectiousness and the development of drug resistance.

2.3 WHAT CAN WE DO?

A comprehensive approach to eliminating or containing the resistant clone is required. Elements of the strategy that have been discussed include: defining and mapping the targeted area(s); reducing transmission through vector control, early diagnosis and treatment, follow-up and radical treatment of treatment failures; reducing drug pressure of the artemisinins on the parasites; targeting the migrant population for malaria control and containment activities; and mass screening and treatment of patients with malaria.

Clearly the optimal strategies over the next 5–10 years must be based on the best available evidence and expert discussions. The next malaria season starts, however, in a few months, so that if there is to be an impact this year, decisions must be taken. Urgent priorities for immediate action are to:

- Set up an organizational structure to facilitate a rapid, coordinated, effective response, including an in-country task force to plan, coordinate and ensure implementation of agreed strategies;
- Maximize coverage with long-lasting insecticide-treated nets and hammock nets in the target area;

- Replace the recommended mefloquine plus artesunate for 3 days with an effective co-formulated antimalarial drug, if necessary by granting 'special case' status for safe and effective drugs that are not yet on the WHO pre-qualification list (selection of the most appropriate drug was one objective of the meeting and is discussed below); and
- Ensure that this drug is rapidly deployed in both the public and private sectors, and remove artemisinin monotherapies.

Other priorities are:

- Operational research to map mobile and migrant populations and target them for appropriate malaria control measures;
- De-registration of artemisinin monotherapies and enforcement of the ban;
- Increased free access to early diagnosis and appropriate treatment, e.g. by village malaria workers (who also act as a community surveillance system);
- Strengthened capacity for surveillance and monitoring;
- Effective behaviour change communication on appropriate antimalarial drug use; and
- Combat against counterfeit and substandard drugs.

3. WHICH ANTIMALARIAL MEDICINE?

Having agreed on the urgent need to consider alternative co-formulated antimalarials for use in western Cambodia, presentations were made, followed by discussions, to select the best option. Neither directly observed treatment with mefloquine plus artesunate for 3 days nor a possible co-formulated combination were considered to be options worth pursuing, as they would not address the known reduced efficacy of mefloquine, because of the poor tolerance and subsequent poor popularity of mefloquine and because of people's continued preference for artemisinin monotherapy, especially in the private sector in Cambodia.

3.1 CURRENT POLICY IN CAMBODIA AND THAILAND

Mefloquine plus artesunate for 3 days is the first-line treatment for falciparum malaria in Cambodia and Thailand. In Cambodia, there is heterogeneity of efficacy, with 28-day failure rates of between 0% and 14.3% (Denis et al., 2006a). The highest failure rates were found in western Cambodia on the Thai–Cambodian border, while efficacy is well maintained in the east. In Thailand, where a 2-day regimen was used until 2007, high failure rates have been observed in the eastern Trat province, on the border with Cambodia (Vijaykadga et al., 2006).

There was initially some confusion as to why the antimalarial drug policy should be changed in the affected region this year. Officials were told that the urgency for change arises from the need to contain the spread of parasites with 'drug resistance' or 'drug tolerance'. This situation is different from the usual one, in which a change in drug policy is recommended on the basis of treatment failures exceeding a cut-off point, when the aim is to reduce morbidity and mortality associated with using an ineffective drug. It was emphasized that any recommendations arising from this meeting were for emergency use on the Thai–Cambodian border this year and would have to be reviewed at the end of the year.

3.2 NON-ARTEMISININ-BASED ANTIMALARIAL VERSUS ARTEMISININ-BASED COMBINATION THERAPY

There are obvious advantages to removing the drug pressure of the artemisinin derivatives on parasites by using a non-artemisinin drug and withdrawing all artemisinin monotherapies. The drug pressure of monotherapies is considerably greater than that of an ACT. With a co-formulated ACT in which the partner drug is effective, parasites never 'see' artemisinin (or the derivative) unprotected by the partner. Although quinine-based combinations with antibiotics were mentioned, there are obvious problems

with compliance and there are no co-formulated products with antibiotics. Realistically, atovaquone–proguanil is the only option, although this combination is vulnerable to rapid development of high-level resistance, as the antimalarial activity of proguanil is very weak. Further discussions on non-artemisinin-based options were therefore limited to this combination.

3.3 DRUG QUALITY

It was decided to discuss the choice of antimalarial drug in this forum because it had become apparent that the optimal choices of co-formulated, safe, effective drugs for use in these circumstances were not currently on WHO's list of recommended or pre-qualified drugs. A special case would therefore have to be made for recommending use of an off-list drug. Nevertheless, it is clearly essential that any such drug should be of acceptable safety, efficacy, quality and stability.

3.4 THE OPTIONS

The advantages and disadvantages of the possible antimalarial drug options were presented. It became clear that only three were viable: artesunate–pyronaridine, atovaquone–proguanil and dihydroartemisinin–piperaquine. This short list was discussed systematically on the basis of several criteria for selection. The options are summarized below and presented in a simplified format (in alphabetical order) in Table 1.

Artemisinin-based combination therapies

Artemether–lumefantrine

Artemether–lumefantrine would be the obvious choice, as it is produced commercially according to good manufacturing practice standards and is readily available, safe and generally well tolerated. It has also been shown to be highly effective in Thailand (efficacy, > 95%) (Hutagalung et al., 2005). It does not work well enough, however, in western Cambodia, with failure rates of 13.5–28.2% in three separate trials; it is therefore not a viable option for Cambodia (Denis et al., 2006b). It is not clear why it is not effective. Drug absorption may be an issue. Cross-resistance between mefloquine and lumefantrine might occur, or the relatively low dose of the artemisinin derivative might be responsible, as the dose of artemether is lower than the equivalent dose of artesunate in mefloquine plus artesunate. This difference is not usually important but might point towards 'resistance' or 'tolerance' to artemisinin.

Artemisinin–naphthoquine

Very little is known about this drug, which is registered in China. The recommended regimen is for only one day. Nothing is known about the quality of the drug. It is clearly not yet ready for wide-scale deployment.

Artemisinin–piperaquine

This co-formulated combination is being used in elimination projects in the Comoros and in Kampong Speu Province in Cambodia. There is therefore some experience with the product, and anecdotal reports indicate that it is well tolerated and effective; there are, however, very few data on its safety, efficacy and quality. The dose of artemisinin might be insufficient, as artemisinin is 5–10 times less active than dihydroartemisinin; therefore, studies are required to prove that it is sufficiently potent. The current lack of data on safety, efficacy and quality mean that this is not a viable option for wide-scale deployment this year.

Artemisone plus a partner drug

Artemisone is currently being tested in a Phase 2 trial by the Medicine for Malaria Venture. It is therefore too early in its development to be considered for deployment.

Artesunate plus antibiotics

There are currently no co-formulated products on the market or being developed.

Artesunate–pyronaridine

This co-formulated drug is in its final stage of development. Phase 2 and 3 trials were conducted in Pailin, and the preliminary results suggest that it is highly effective and well tolerated. An additional advantage is that pyronaridine has a shorter half-life than piperaquine and might therefore be less susceptible to resistance. Although it is expected to be registered with the European Medicines Agency and/or the United States Food and Drug Administration by the end of 2008, it is not yet ready for submission and is not yet produced commercially. It is therefore unlikely to be available for wide-scale deployment. It is nevertheless a very promising option and might be the drug of choice once it is registered and commercially produced.

Dihydroartemisinin–piperaquine

Co-formulated dihydroartemisinin–piperaquine is registered in Cambodia, where it is already being used in Pailin in the public sector; it has been used by village malaria workers for four years. It is one of the first-line drugs in Viet Nam. Reports from all parts of South-East Asia indicate that it is highly effective and well tolerated (Myint et al., 2007). It is being considered for recommendation by the WHO Global Malaria Programme and is expected to be registered by the European Medicines Agency and/or the Food and Drug Administration by mid-2008. Several marketed products of variable quality are available. A disadvantage of its use in a low transmission setting is that piperaquine has a very long half-life. There is also concern about the stability of dihydroartemisinin (Haynes et al., 2007; Jansen, Soomro, 2007). On balance, however, dihydroartemisinin–piperaquine emerged as the best option for deployment this year.

Non-artemisinin-based combination therapies

Atovaquone–proguanil

The major potential advantage of this combination is that it does not contain an artemisinin and therefore theoretically would not exert further pressure on this class of drugs. It is made to good manufacturing practice standards and has been used mainly for prophylaxis and treatment in travellers, in whom tolerance is good and few failures have been reported (Musset et al., 2006). In Thailand, where the drug is registered, 140 cases were treated, with a 98% cure rate (Krudsood et al., 2007). Nevertheless, proguanil is weakly effective on its own, posing a challenge to the definition of the drug as 'combination therapy'. It has less effect on gametocyte carriage than ACTs. It has never been used in Cambodia.

The main arguments for not recommending deployment of atovaquone–proguanil were the fact that absolute resistance to atovaquone is encoded by a single mutation and can therefore emerge very quickly and the cost of the drug, which is currently around US$ 50. This in itself should not, however, obviate its consideration as a viable option.

Quinine plus antibiotics (e.g. doxycycline, azithromycin, clindamycin, fosmidomycin)

There are currently no co-formulated quinine-based combinations. In addition, quinine is poorly tolerated and requires a 7-day regimen, which is rarely adhered to.

3.5 DRUGS TO BLOCK TRANSMISSION

The role of primaquine in blocking transmission was also discussed. Artemisinins are some of the most potent transmission blocking drugs, and the additional benefit of primaquine is under investigation (El-Sayed et al., 2007; Shekalaghe et al., 2007). For instance, addition of primaquine to treatment with atovaquone–proguanil would be important.

There was some uncertainty about its safety in view of the high prevalence of glucose-6-phosphate dehydrogenase deficiency in the region. It has been reported that 80–85% of deficiency for this enzyme in Cambodia is of

the Vien Chang variant, which is very mild with little haemolysis. In the Kampong Speu eradication project, a single dose of 9 mg was given, apparently with no problem, and use of a single-dose treatment in Thailand has also been unproblematic. Although the meeting did not make a clear recommendation, it was suggested that, if primaquine were used, a single dose of 0.5–0.75 mg/kg given on the first day under directly observed therapy would be sufficient and should be safe.

Brief mention was made of the new 8-aminoquinoline drug, tafenoquine, which is, however, still under development.

3.6 RECOMMENDATIONS

The meeting concluded that it could endorse co-formulated dihydroartemisinin–piperaquine for use this year on the Thai–Cambodian border. This decision was made on the basis that it is the co-formulated antimalarial drug that fulfils the most important criteria, in particular safety, efficacy, tolerability, availability and the likelihood of registration by the European Medicines Agency and the Food and Drug Administration in the near future. WHO will ensure that the available products undergo accelerated quality assessment.

There may also be arguments for using atovaquone–proguanil in addition to dihydroartemisinin–piperaquine under specific circumstances, such as mass screening. The role of primaquine in reducing transmission and its suitability for widescale deployment should be the subject of further research, especially with regard to glucose-6-phosphate dehydrogenase deficiency.

Table 1. **ANTIMALARIAL MEDICINE OPTIONS**

	Safety	Efficacy	Good manufacturing practice	Commercially produced	Acceptability/ tolerability	Local familiarity	Resistance	Action against gametocytes	Cost (per adult course) (US$)
Artemisinin–piperaquine	Unknown	Yes	No	Yes	Unknown but anecdotally yes	Clinical trials in Cambodia	Little pressure on both partner drugs, as both still effective	Yes	< 2
Artemether–lumefantrine	Good	Yes, in Thailand No, in western Cambodia	Yes	Yes	Yes	Clinical trials in both Cambodia and Thailand	Cross-resistance between mefloquine and lumefantrine	Yes	< 2
Artesunate–mefloquine	Good but unpleasant side-effects	Decreasing in both Cambodia and Thailand	Problems in quality of local re-packaging of drug in Cambodia	No as a co-formulation	Low in Cambodia Good in Thailand	Yes, current policy in both Cambodia and Thailand	Not co-formulated; therefore use of monotherapy puts high pressure on artemisinins	Yes	~ 5 (including packaging)
Artesunate–pyronaridine	Data limited but good so far	Data limited but good so far	Under review	No	Data limited but good so far	Clinical trials in Cambodia	Little pressure on both partner drugs, as both still effective	Yes	< 2
Dihydroartemisinin–piperaquine	Good	Good	Under review	Yes	Yes	Yes in Cambodia Clinical trails in Thailand	Little pressure on both partner drugs, as both still effective	Yes	< 2
Atovaquone–proguanil	Good	Good, but most data on travellers	Yes	Yes	Yes Anecdotal reports of poor tolerance in Thailand	None in Cambodia Clinical trials in Thailand	Theoretically no drug pressure on artemisinins Resistance to atovaquone can emerge quickly Proguanil not effective on its own	No	++ Donation?

4. ROLE OF DIAGNOSTICS

4.1 IN ROUTINE TREATMENT

In this region, which is a focus of multidrug-resistant malaria, it was recommended that all malaria cases should be confirmed biologically before treatment, for better case management and to limit overuse of drugs. While this is largely the case in Thailand, it is very difficult to enforce in Cambodia because of the major role played by the unregulated private sector.

The reported large proportion of malaria cases due to *P. vivax* in certain areas of Thailand and in western Cambodia requires that the choice of rapid diagnostic tests be reviewed.

4.2 IN MASS COMMUNITY-BASED INTERVENTIONS

There was less agreement at the meeting on whether populations should be screened before treatment in the context of a mass elimination campaign. In order to implement a 3-day treatment and to reduce unnecessary use of drugs and the associated risks and costs, ideally, only those people who are parasitaemic should be treated. Use of a rapid diagnostic test detecting *P. falciparum* and pan-malaria antigens is attractive from the point of view of speed and efficiency but runs the risk of missing low parasitaemia and gametocyte carriers, with obvious consequences in terms of continued transmission. Concern was expressed that use of microscopy would mean that people at very early stages of infection or with asymptomatic infections would be missed, even if it were practically feasible. This led to a discussion on the possible role of PCR. This area needs further clarification.

5. VECTOR CONTROL

5.1 VECTOR TYPE

The importance and challenge of tackling the vector in the 'forest malaria' context were emphasized. ELISA, used to detect the circumsprozoite protein in head and thorax, is the basic method for incriminating vector species and for determining their importance in malaria transmission. Confirmation by PCR is required, as many false-positive results are obtained for *P. falciparum*, particularly in zoophilic anophelines. The main vectors in Cambodia are *An. dirus sensu stricto*, 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 forested areas in Pursat, whereas *An. minimus* predominates in changing environments on the forest fringe and in areas of recent deforestation in Pailin. *An. babirostris* was also confirmed as a malaria vector. In view of the low level of *P. falciparum* transmission, serology might be more appropriate for tracing the dynamics of transmission during the intervention.

5.2 VECTOR BEHAVIOUR

Trends in resting behaviour

A study of indoor resting behaviour in Cambodia and Viet Nam suggested very low ratios of indoor to outdoor resting for all vectors but particularly for *An. dirus* and *An. maculatus*. As *An. dirus*, when biting indoors, often rests briefly on walls before feeding, indoor residual spraying would not be very effective (Truong et al., 2005).

Timing of biting behaviour

A study of hammock nets showed that a significant proportion of bites occur before 22:00. This was particularly true for *An. maculatus*, with which 56% of bites occurred before 22:00, as compared with 36% for *An. dirus* and 28% for *An. minimus*.

Trends in endophagy

Biting indoors in open housing structures was generally much more frequent than in closed structures. This difference was particularly notable for *An. minimus*, with a biting rate of 7.9 in open housing and 0.6–1.4 in closed structures. This compares with 1.3 versus 0.3–0.6 for *An. dirus*.

5.3 PARASITE PREVALENCE RATES

A study of parasite prevalence in Pailin and Pursat suggested that more than 80% of cases of parasitaemia were asymptomatic and that the majority of infections were due to *P. vivax* rather than *P. falciparum*.

5.4 OPTIONS FOR VECTOR CONTROL

Vector control is challenging because the vectors are predominantly exophilic and exophagic, and many bite in the early evening.

Insecticide-treated nets

As most vectors bite after 22:00, nets can clearly be protective. Although the majority of people sleep under nets, most of the 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 of the long-lasting type.

Insecticide-treated hammocks and hammock nets

Men who go to the forest often sleep in hammocks, and people in villages often sit in hammocks before sleeping time. Insecticide-treated hammocks and hammock nets have therefore been designed, to be used during sleeping time but also for protection while sitting in the hammock in the evening. Olyset® hammocks were found to be more protective than control hammocks by 44% against *An. minimus*, by 46% against *An. dirus* (but only at the end of the rainy season) and by 50% against *An. maculatus* (but only in Pailin). These figures are probably underestimates of the personal protection provided, as mosquitoes were collected only on persons in the sitting position. Long-lasting insecticide-treated hammocks were also found to be effective in West Africa (Hougard et al., 2007), suggesting that complete coverage of the forest worker population with insecticide-treated hammocks and nets should be the aim. Long-lasting insecticide-treated hammocks would be preferable as they also protect against vectors that bite before sleeping time (56% of *An. maculatus*, 36% of *An. dirus* and 28% of *An. minimus*).

Insecticide-treated materials

In order to increase personal protection, other appropriate insecticide-treated materials, such as blankets and clothing, should be designed, and the engagement of industry in this process should be encouraged.

Indoor residual spraying

As the vectors are predominantly exophilic and exophagic, indoor residual spraying has a limited effect, and only small endophilic fraction vectors are killed during their brief rest inside a house. It is therefore recommended only as an adjunct to insecticide-treated nets, where feasible. If a pilot project is to be conducted, the outside walls should also be sprayed, and the target should be 100% coverage of all village houses and forest plots. This would require huge resources that could be used more effectively elsewhere.

Repellents

The role of repellents in personal protection was discussed as a means of bridging the gap in vector control. Although a recent study in South America showed promising results (Hill et al., 2007), the data are limited. If such complementary interventions are to be used, they should be tested in pilot studies, with adequate assessment of their quality and safety, and should be accompanied by appropriate behaviour change and communication to ensure proper use.

Larvicides

An. maculatus and *An. dirus* breed in small pools and *An. minimus* in small streams. Therefore, it would be very difficult to control larvae with larvicides and environmental control measures.

Fogging

Although fogging has been used to control dengue and malaria in Thailand and could be an effective means of dealing with these exophilic vectors, it must be repeated every other day and is therefore not practical at this stage.

5.5 RECOMMENDATIONS

Long-lasting insecticide-treated nets, hammocks and hammock nets should be deployed rapidly and widely with the aim of 100% population coverage.

Indoor residual spraying is recommended for malaria vector control only in addition to insecticide-treated nets, where feasible. If it is used, outside walls should also be sprayed.

The use of other measures of personal protection, such as long-lasting insecticide-treated hammocks, repellents and other insecticide-treated materials should be explored.

6. MASS SCREENING AND TREATMENT

6.1 THE 'PROACTIVE MALARIA CONTROL' PROJECT

The 'Proactive Malaria Control' project is based on mass screening and treatment of the entire population in Pailin, Sampouv Loun and Samlot. Two campaigns were proposed, to be carried out at the end of 2008 or early 2009, in the low transmission season. During the campaigns, the entire population of the target area will be screened for malaria with a rapid diagnostic test, and those found to have malaria will be treated with an antimalarial medicine under directly observed therapy. Addition of primaquine is being considered. It was suggested that complete coverage with long-lasting insecticide-treated nets be undertaken at the same time, if not already achieved, and passive and active surveillance will be undertaken, especially of the migrant population. During the campaigns, people who have been screened will be marked with indelible ink to identify them. It was unclear whether the aim of the campaigns was to reduce the burden of infection in the community (and subsequently the opportunity for an infected person to travel elsewhere) or to eliminate transmission.

6.2 DISCUSSION POINTS

Diagnostic screening or no screening

Concern was expressed that rapid diagnostic tests would not be sufficiently sensitive to identify carriers with low parasite densities and gametocyte carriers. The advantages and disadvantages of microscopy, PCR and fluorescent microscopy were discussed. Use of microscopy was considered impracticable.

The alternative—mass treatment without screening—was also discussed. The advantage would be that all potential infections are treated, whether or not they are detectable. There was no consensus on this approach, as it did not seem feasible for a 3-day regimen on a full population basis.

Timing

The meeting discussed whether targeting the low transmission season alone was adequate to ensure complete interruption of transmission. The campaigns should ideally be carried out in the high transmission season as well, although, as this is the rainy season, it would be logistically very difficult to carry out successfully. The rationale of conducting the campaigns within a 2-week period was questioned, except as it applied to the longevity of 'indelible' ink.

6.3 HUMAN MOVEMENT

In addition to incomplete coverage with treatment due to false-negative diagnoses, concern was raised about the degree of population movement in and out of the area throughout the year. The overall strategy should include activities targeted at mobile and migrant populations (estimated at 25%).

7. OPERATIONAL ISSUES IN CAMBODIA

7.1 CONTEXT

To clarify some of the operational issues that will affect the choice and feasibility of strategies, a brief socio-political description was presented.

In 1979, the Pol Pot regime officially came to an end, and the Khmer Rouge retreated mainly to Pailin (at that time, part of Battambang Province) and Odder Meanchay. These therefore became major Khmer Rouge strongholds and resource centres, even after the death of Pol Pot in 1998. As part of the peace process, Pailin became a municipality and Odder Meanchay became a province in 2001; however, they began to receive Government support only after the 2003 elections, due to security problems. Since the establishment of peace and stability and the opening up of these areas, there has been a large influx of settlers from other provinces. The national elections scheduled for July 2008 will affect the ability to carry out malaria control activities. A policy of decentralization is being implemented in 2008.

7.2 DEFINING THE POPULATION DENOMINATOR

Accurate planning is difficult because of a lack of accurate population estimates. The last population census was held in 1998, although data collection was incomplete in Khmer Rouge strongholds, especially Pailin and Odder Meanchay. The annual population projections of the National Institute of Statistics of the Ministry of Planning are based on the 1998 census, and the Ministry of Health generally uses these data; however, there are wide discrepancies between these estimates and those from other sources. For example, according to the malaria control programme, which updates the populations at risk annually in villages classified as endemic (within 2 km of a forest), there were 54 088 people at risk, whereas the National Institute of Statistics estimate for the municipality was only 36 545. A new census is about to start, and draft results are expected in October 2008. It may be possible to cooperate with the census takers to obtain data as early as possible.

7.3 HEALTH-CARE INFRASTRUCTURE

In Cambodia, the second subnational administrative unit is the district. After health sector reform in 1997–2001, the Ministry of Health implemented a plan based on operational districts covering populations of about 100 000; these can cover several administrative districts or parts of them. The target is one referral centre per operational district, one health centre

per 10 000 population, and health posts in the most remote areas servicing 2000–3000 people. All public health facilities in Cambodia charge user fees, which are low in operational districts but can be significant in referral hospitals. To increase access, the Ministry of Health has introduced an equity fund with World Bank support. Actual use of public health facilities is low (around 20% according to surveys), most people choosing to use the private sector. Although the public health sector is gradually being strengthened, issues of access must be further addressed. To improve the management of health services in operational districts in remote areas, the Government is temporarily outsourcing management to nongovernmental organizations, supported by the Asian Development Bank, presumably with success.

The infrastructure of the public health system in former Khmer Rouge strongholds is weak because of their long seclusion and late central Government support, and the number of qualified staff is limited. Pailin receives support mainly from the Health Sector Support Project (Asian Development Bank, World Bank, United Kingdom Department for International Development) and the United Nations Population Fund. Initiation of infrastructure support (construction) from the Health Sector Support Project is planned later in 2008. No major nongovernmental organization appears to be active in the area. Médecins sans Frontières set up a malaria control project in 2003, which has been handed over to Family Health International.

7.4 COMMUNITY INFRASTRUCTURE

Villages are grouped into communes, which have councils that are recognized as part of the Government system. Each has a chief of commune and a person responsible for various areas, such as health.

The Ministry of Health recognizes village health support groups, consisting of two persons per village. The level of activity varies greatly. The malaria programme targets 3200 villages located within 2 km of a forest. In 1000 villages, there are village health volunteers, who are responsible mainly for preventive activities: health education, net impregnation and referral of possible malaria cases to the health centre. In 315 villages, there are village malaria workers, supported by the Global Fund, who diagnose *P. falciparum* malaria with a rapid diagnostic test and treat patients. In 2006, village malaria workers treated 45 000 confirmed cases of falciparum malaria, which is higher than the number of confirmed malaria cases reported by the

public health facilities during the same period. In addition, nongovernmental organizations support village health volunteers in four malaria-endemic provinces (Health Unlimited and Partners for Development) and 22 village malaria workers in Pailin (Family Health International).

7.5 PRIVATE SECTOR

The official private sector consists of licensed drug outlets and providers. There are two categories of registered pharmacy: qualified and semi-qualified. In addition, there are private hospitals, clinics and laboratories. There are also numerous unlicensed drug outlets and providers, including markets stalls, general shops, street vendors and traditional healers. Population Services International has been responsible for training private providers and for social marketing of mefloquine plus artesunate for 3 days (Malarine®) and rapid diagnostic tests (Malacheck®). In Pailin, 75 private providers were trained by Population Services International in 2004 and 41 in 2005.

7.6 MOBILE POPULATIONS

More than 200 000 Cambodians cross the Thai border every year, to work on rubber plantations and in fruit orchards, and for business, family visits, tourism and health care. In Thailand, the vast majority of malaria cases in foreign nationals occurred on the Thai–Myanmar border (93%), with only 2.5% on the Thai–Cambodian border. Even on the Thai–Cambodian border, in Trat Province, only 70% of malaria cases were in foreigners from Cambodia and 25% in travellers from Myanmar. This has obvious worrying implications for the rapid spread of resistant clones across Thailand and into Myanmar.

In 2006, malaria cases among Thai nationals occurred mainly on the border with Myanmar (63%), with 24% on the border with Malaysia, 11% on the border with Cambodia and the remainder on the border with the Lao People's Democratic Republic.

8. ISSUES FOR CLARIFICATION

The meeting discussed 'Why?' and 'What?' to do, and also issues pertaining to 'Where?' 'Who?' 'How?' and 'When?'.

8.1 WHERE (TARGET AREA)?

The geographical extent of spread must be defined urgently, and an effective surveillance system must be put in place to define where containment activities should be targeted. Concern was expressed that limiting the area of targeted interventions to Pailin and neighbouring districts would be insufficient. In addition to data on the extent of spread, the size of the areas to be targeted with different modalities must be determined.

Proven interventions, such as long-lasting insecticide-treated nets and effective co-formulated drugs, should be deployed rapidly across a wide geographical area—either the whole Thai–Cambodian border or nationwide. It is worth bearing in mind that a single national change in antimalarial policy will be much easier to implement than instituting different policies for eastern and western Cambodia.

In addition to these interventions, intense containment efforts should be targeted at smaller, defined 'epicentres' to maximize the chances of eliminating the parasite. In these areas, new interventions, such as mass screening and treatment, mobile outreach teams and extra personal protection should be used, with appropriate monitoring.

8.2 WHO?

Planning and coordination

An organizational structure must be set up to ensure a rapid, coordinated, effective response. This will require multisectoral partnerships at global, regional, national and community levels. At each level, key stakeholders should be identified and involved, including other international agencies (e.g. the World Food Programme, UNICEF, the International Organization for Migration), government departments (e.g. drugs, food, customs, police), nongovernmental organizations and community organizations. At global and regional levels, WHO should assume coordination and leadership. Two further meetings to be held in Bangkok are being organized by WHO. At national level, a task force should be set up to manage operations. Given the importance of high-level political commitment, the task force should be chaired by a high-level official of the Ministry of Health and/or WHO.

Implementation

There is a lack of trained staff, particularly at provincial and district levels. The additional human resources required to implement any strategy for containment must be addressed. This will obviously be influenced by and will influence decisions on how operations are to be implemented, as discussed below.

8.3 HOW (CAMPAIGNS OR EXISTING INFRASTRUCTURE)?

Having identified the ideal technically sound strategies to contain drug resistance on the basis of current knowledge, the best means for implementation will be determined according to practicalities, in particular, whether the necessary infrastructure exists to implement and sustain activities, or, if not, whether it can be built up quickly enough for an effective response or whether an extraordinary campaign will be required. The managing and financing of these activities must also be addressed.

The infrastructure in Cambodia is still weak, and additional resources will almost certainly be required to implement the strategies. This could have a positive effect, by helping to build general capacity for disease surveillance and management, or, conversely, could draw scarce resources from other areas.

Several campaigns have been conducted in Cambodia, including that for immunization and the very successful schistosomiasis elimination campaigns. Substantial resources are being poured into rapid response teams for avian influenza, and possible collaborations should be explored.

8.4 WHEN?

The malaria season starts in May and peaks in October. The rainy season usually starts in June, after which access becomes difficult, especially to remote areas. The next delivery of long-lasting insecticide-treated nets is not scheduled until June. If a new drug policy is to be operationalized in time for this year, we must act extremely fast. Drugs must be sent to Cambodia by April and delivered in May.

8.5 OTHER ISSUES

The private sector

A long-term strategy for the private sector in Cambodia is required. In the meantime, both incentives and regulatory approaches are advocated with regard to the sale of artemisinin monotherapies and substandard drugs. This could involve the accreditation of trained sellers and a supply of heavily subsidized, good-quality co-formulated drugs and legislation and enforcement of a ban on unregistered products.

The strategy for Thailand

The meeting emphasized that, although many of the discussions focused on Cambodia, the situation in Thailand should also be considered. Thailand has a highly developed system for malaria control, with an extensive network of services and facilities offering free diagnosis and treatment to both Thai and foreign nationals. The private sector is tightly regulated, and the sale of mefloquine and artemisinins is forbidden. As the burden of malaria in Thailand is low, however, it is not a high priority for public health, and resources are lacking, especially at the peripheral level. In order to contain drug resistance by eliminating malaria on the Thai–Cambodian border, stakeholders should be involved, and additional resources are required to build capacity, especially at provincial and district levels.

9. PRIORITIES FOR RESEARCH AND DEVELOPMENT

SURVEILLANCE

- Define the geographical extent of spread with more studies on drug resistance (planned).
- Map at-risk populations, drug resistance, health-care infrastructure and other elements in Cambodia.

MIGRANTS

- Map the migrant populations in Cambodia and Thailand.
- Conduct operational research on optimal strategies for targeted control.

DRUGS

- Conduct studies of pharmacokinetics (increasing dose, splitting dose).
- Determine the safety and efficacy of primaquine, with assessment of the prevalence of glucose-6-phosphate dehydrogenase deficiency.
- Conduct research and development of non-artemisinin-based combinations.
- Study substandard and counterfeit antimalarial drugs along the Thai–Cambodian border (planned).

DIAGNOSIS

- Determine the optimal diagnostic strategy in view of the increasing proportion of cases of *P. vivax* malaria.

VECTOR CONTROL

- Conduct entomological studies to define areas of local transmission (including serology).
- Conduct research and development of repellents and insecticide-treated materials.

HUMAN BEHAVIOUR

- Determine the current treatment-seeking behaviour and antimalarial drug use (planned).
- Provide optimal information and education and bring about behaviour change to improve care-seeking.

ANTIMALARIAL DRUG SUPPLY

- Determine ways of ensuring that only high-quality co-formulated drugs are available (planned).
- Understand the distribution network, availability and cost of antimalarial drugs (planned).

FOREST MALARIA

- Conduct an in-depth study of parasite–vector–host factors in forest malaria.

RESERVOIR

- Conduct research on the importance of the human reservoir before and during an intervention (with PCR methods).

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